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CONTENTS

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GOLD THERAPY IN RHEUMATOID ARTHRITIS

FINAL REPORT OF A MULTICENTRE CONTROLLED TRIAL*

ARRANGED BY

THE RESEARCH SUB-COMMITTEE OF THE EMPIRE RHEUMATISM COUNCIL†

Introduction

In the earlier report of the first 18 months of this trial (Empire Rheumatism Council, 1960), it was shown that, by all criteria except radiological, patients with active rheumatoid arthritis treated over a period of 5 months with a total dose of 1 g. sodium aurothiomalate (Myocrysin) fared better than those treated with a total dose of 0·01 mg. of the same substance given in a "double blindfold" trial over the same period. These patients have now been followed for a further year, *i.e.* for 2 full years since the last injection was given and for 30 months since the start of the trial. What follows is the final report on this multicentre double-blind controlled trial of the effects of gold in rheumatoid arthritis.

* Presented at a meeting of the Heberden Society on December 2, 1961.

† The following have served as Members of the Research Sub-Committee at some time during the period covered by this trial:

Ex Officio

Dr. W. S. C. Copeman (*Chairman of the Council*)
Dr. O. Savage (*Hon. Med. Secretary*)
Dr. R. M. Mason (*Deputy Hon. Med. Secretary*)
Dr. E. Lewis-Faning (*Hon. Med. Statistician*)
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Dr. J. H. Humphrey
Dr. G. D. Kersley
Mr. G. Lloyd-Roberts
Prof. N. F. Maclagan
Prof. G. A. Smart
Dr. H. F. West

The report was prepared jointly by Dr. F. Dudley Hart (Chairman at the initiation of the trial) and Dr. E. Lewis-Faning (Hon. Med. Statistician to the Empire Rheumatism Council), with the assistance of all members of the Research Sub-Committee. The *x*-ray films were assessed by Dr. Ifor Pennant Williams.

Losses to the Trial (Table I, overleaf)

In the previous report—based on the findings during the first 18 months—nine out of 99 patients treated with gold and five out of 100 controls‡ were excluded because they had received less than half the injections, or had changed treatment because of deterioration, or had failed to attend for assessment (Table I). The analysis at Month 18 was therefore based on ninety patients in the gold-treated series and 95 controls. No interim assessments were made between the 18th and 30th months, and at the latter assessment a further thirteen from each series had been lost to the trial. The reasons for the losses in both periods are shown in Table I.

Since the purpose of this report is to compare the gold and control series 30 months from entry to the trial, *i.e.* 2 years after *completing* the course of treatment, this analysis is based on a follow-up of 77 patients in the gold series and 82 controls.

Second Courses of Therapy

Initially it was agreed that after Month 18 assessment a second course of injections of the same type could be given at the discretion of the physician in charge. Such second courses were requested for sixteen of the gold series and twenty of the controls.

Two of the controls given second courses were subsequently withdrawn: one developed cancer of the cervix; and the other developed albuminuria after six injections of the second course, deteriorated rapidly, and becoming progressively crippled was started on prednisolone.

A comparison of the subsequent progress of those who did and did not receive a second course is made in a later section of this report.

‡ Although the term "controls" is used for the series of patients receiving the smaller dose of gold, this does not imply that the changes and complications occurring therein can with certainty be considered simply as part of the natural history of rheumatoid arthritis.

TABLE I

LOSSES FROM THE FOLLOW-UP OF PATIENTS IN THE TRIAL

Exclusions		Series	
		Gold	Control
(1) From 18-month Analysis	Toxicity and less than half the injections	3	2
	Deterioration involving change of treatment	1	1
	Failed to attend for assessment at Months 12 and 18	5	2
	Total	9	5
(2) Additional from 30-month Analysis	Deaths (Gold at 12* and 15* mths; Control at 29 mths)	2	1
	Concurrent disease (cancer of cervix)	—	1
	Deterioration involving change of treatment	10	6
	Failed to attend for assessment at Month 30	1	5
	Total	13	13
Total Losses up to Month 30		22	18
No. available for analysis at Month 30		77	82

* Included to 12 months in the previous (18-month) report; in neither case was gold therapy considered responsible for death.

TOXICITY (Table II)

The incidence of toxic effects can be measured as:

(*i*) The number of persons who experienced at least one toxic reaction, expressed as a percentage of the number at risk,

or

(*ii*) The number of toxic reactions recorded per patient at risk.

(*i*) *Persons Experiencing at least One Toxic Reaction.*—Arising out of the first course of therapy, toxic reactions were recorded in 35 per cent. of the 99 patients on gold and in 16 per cent. of the 100 controls.

From the second course of therapy given after 18 months in the trial, three (19 per cent.) of the sixteen receiving gold and one (5 per cent.) of the twenty controls had side-effects (Table II). Two of those on gold had also experienced toxicity in the first course. (Further details of these are given on p. 317, para. 1.)

All these reactions occurred during the period of injections, with the one exception of a patient on gold who developed purpura and hepatitis 6 months after completing the first course, suffered a severe relapse of the rheumatoid arthritis, and was admitted to hospital for a period of 5 months.

Because of these reactions, fourteen of the 35 gold-treated reactors and four of the sixteen control reactors failed to complete the first course of injections. Only one patient failed to complete the second course—a

TABLE II

INCIDENCE OF TOXIC REACTIONS

Course		First		Second	
Series		Gold	Control	Gold	Control
Total Entrants		99	100	16	20
(*i*) Toxic Reactions	At least one toxic reaction	35(35%)	16(16%)	3(19%)	1(5%)
	No reaction	64	84	13	19
(*ii*) Complications Recorded	Dermatitis (hospitalized)	4	—	—	—
	Dermatitis (less severe)	17	7	1	—
	Purpura (hepatitis in one patient)	2	1	—	—
	Albuminuria	4	3	1	—
	Amyloidosis	—	—	—	1
	Stomatitis or gingivitis	3	2	1	—
	Oedema and malaise	1	3	—	—
	Corneal ulcer or keratitis	2	—	—	—
	Fever	1	—	—	—
	Flare of arthritis	1	1	—	—
	Ulcer or haematemesis	2	—	—	—
	Dyspepsia	3	—	—	—
	Total Complications	40	17	3	1
Complications per Patient		0·40	0·17	0·19	0·05

control patient who developed signs of amyloidosis after six injections.

(*ii*) *Mean Number of Toxic Reactions per Patient.*—During the initial course of injections, five patients on gold and one of the controls each reported two complications, so that there were forty complications in all for the gold series and seventeen for the control series, *i.e.* the mean number of complications per patient was 0·40 and 0·17 for the gold and control series respectively. Comparable rates for the second course were 0·19 and 0·05, the lower levels for the second course being due, at least in part, to the fact that only six of the 35 on gold and only three of the sixteen controls who had reactions on the first course of therapy were amongst those for whom a second course was requested.

Types of Reaction

The toxic reactions recorded on the first course (gold 40, control 17) are listed in Table II. Dermatitis was the most frequent type of reaction (gold 21, control 7) and in four of those on gold was severe enough to require admission to hospital.*

Apart from these skin reactions, toxic effects were infrequent (gold 19, control 10). They included four cases of albuminuria in the gold series as compared with three in the control series.* The fact that more cases of oedema were reported in the controls than in the gold series (gold 1, control 3) accords with the results in another trial (Meanock and Lewis-Faning, 1961) and reminds us again that this condition is frequently a feature of the disease rather than a side-effect of the treatment.

There were fourteen in the gold series and four controls in whom injections were stopped because of toxic reactions. The former comprised ten cases of dermatitis (including the four admitted to hospital) and one case each of stomatitis, oedema, corneal ulcer, and buccal ulcer. Three of the four control reactors who did not complete the injections had dermatitis, and one had albuminuria.

Three patients developed toxic reactions during or after the second course of gold. One, who was free from reaction in the first course, developed dermatitis 2 weeks after the final injection of the second course. The second, who had had albuminuria in the first course, experienced stomatitis in the second, and injections were stopped for 3 weeks. The third had albuminuria during both courses—after the seventeenth injection in the first and after the fourteenth in the second.

In the control series only one reaction in the second course was reported—this was the patient referred to above (p. 317) who developed signs of amyloidosis after six injections.

Sensory peripheral neuropathy confined to the lower extremities was reported in only two patients, both at Month 30 (gold 1, control 1).

In this study, therefore, 35 per cent. of the gold-treated cases and 16 per cent. of the controls developed toxic side-effects during the first course of therapy. These led to withdrawal from therapy in fourteen of the gold-treated cases, four of whom needed admission to hospital, and in four of the controls. During the second course, 19 per cent. of those receiving gold (3 of 16) and 5 per cent. of the controls (1 of 20) suffered toxic effects, injections being stopped only in the one control case. Side-effects were clearly more frequent in the gold series, but were seldom serious or severe.

The relation between toxicity and therapeutic effect is examined in a subsequent report (p. 335).

Comparison of Gold and Control Series at the Start of the Trial

Tables III and IV (overleaf) show that the two series were similar at the start of the trial in respect of all factors examined. This was true for all entrants (gold 99, control 100), for those followed to 18 months (gold 90, control 95), and for the somewhat smaller group followed to 30 months (gold 77, control 82). The mean levels for both groups were little affected by the interim losses.

A comprehensive series of statistical tests demonstrated that neither the losses from the trial up to 18 months, nor subsequent losses up to 30 months prejudiced the *initial* similarity of the two series. The omission of eleven patients on gold and seven controls whose treatment was changed because of deterioration may, however, have introduced some bias in the subsequent results of the follow-up, though any such bias was present about equally in both series. In the earlier analysis (to 18 months) group assessments, both including and excluding cases in which treatment was changed, did not differ materially.

Differences referred to throughout the report are considered to be statistically significant only if they attain the 0·05 probability level. No such differences could be demonstrated from the data in Tables III and IV.

* See previous report for details.

TABLE III

SIMILARITY OF THE GOLD-TREATED AND CONTROL SERIES AT START OF TRIAL

Factors Compared		Excluding Withdrawals up to 18 Months		Excluding all Withdrawals up to 30 Months	
		Gold	Control	Gold	Control
No. of Patients		90	95	77	82
No. of Males		26(29%)	27(28%)	22(29%)	23(28%)
Age (yrs) (Mean ± S.E.)		48·7±0·98	48·6±0·98	48·5±1·08	48·4±1·07
Duration of Symptoms (yrs)	1 to 3	59(66%)	65(68%)	49(64%)	56(68%)
	3 to 5	31(34%)	30(32%)	28(36%)	26(32%)
Type of Onset	Acute	29(32%)	25(26%)	27(35%)	20(24%)
	Non-Acute	59	70	49	62
	Not Known	2	—	1	—
Number of Joints Involved (Mean ± S.E.)		17·3±0·92	19·2±0·95	17·6±1·00	18·2±0·98
Functional Capacity ("Mean")*—Physician's Assessment (Grade)		2·3	2·2	2·3	2·2
Fitness ("Mean")—Estimated by Patient (per cent.)		59·5	60·2	60·1	60·7
Strength of Grip (Mean ± S.E.)	Right	144·5	144·8	148·1	146·0
	Left	148·9	144·8	149·7	145·3
Haemoglobin Concentration (g. per cent.) (Mean ± S.E.)		12·4±0·17	12·3±0·15	12·3±0·19	12·3±0·17
Erythrocyte Sedimentation Rate (mm./hr Westergren) (Mean ± S.E.)		41·6±2·07	37·9±1·96	42·3±2·35	38·8±2·32
S.C.A.T.† (per cent.)	Negative −5 to −3	2	7	3	7
	Negative −2 to −1	21	14	23	15
	Positive 0 to +1	22	26	19	23
	Positive +2 to +3	24	23	25	24
	Positive +4 to +7	17	17	16	20
	Not Known	13	13	14	11

* The use of the term "Mean" here and in Tables IV and V is unjustifiable statistically, but convenient as an index to summarize the distributions.
† Minimal positive titre at each centre = 0 (see also under Results—S.C.A.T.).

TABLE IV

SIMILARITY OF THE TWO SERIES AT START OF TRIAL

(A) Functional Capacity (Physician's Estimate),† showing percentage in each grade

Series		Grade					
		1 (Best)	2	3	4	5	Mean*
(*a*) Gold 90; Controls 95 (*i.e.* excluding withdrawals up to 18 months)	Gold	9	53	34	3	—	2·3
	Control	12	57	32	—	—	2·2
(*b*) Gold 77; Controls 82 (*i.e.* excluding withdrawals up to 30 months)	Gold	10	52	34	4	—	2·3
	Control	11	60	29	—	—	2·2

† For definition of grades see previous report.
* See footnote to Table III for use of term "Mean".

(B) Percentage Fitness (Patient's own Estimate)

Series		Fitness (per cent.)					
		100	75	50	25	1	Mean
(*a*) Gold 90; Controls 95 (*i.e.* excluding withdrawals up to 18 months)	Gold	3	42	44	10	—	59·5
	Control	5	40	46	8	—	60·2
(*b*) Gold 77; Controls 82 (*i.e.* excluding withdrawals up to 30 months)	Gold	4	42	45	9	—	60·1
	Control	6	40	44	10	—	60·7

Results

Comparison of Progress in the Two Treatment Series

In the previous report the progress of the two treatment series at Months 0, 1, 3, 6, 12, and 18 was tabulated, analysed, and compared. In the present report the data presented will be those relating to Months 0, 18, and 30 only.

Functional Capacity (Table V)

This was estimated by the physician in five grades.* Table V shows the percentage with given grades of severity at Months 0, 18, and 30 in each series. The "mean"† grades (last column) indicate that both groups were improved in function at 18 months, but that subsequently there was no change.

Detailed examination shows that, at the start, 10 per cent. of both series were in Grade 1, *i.e.* the highest functional grade—fully employed or employable in normal work and able to undertake normal physical recreation. At Month 6 (end of the injection period) 41 per cent. of the gold series as compared with 23 per cent. of the control were in this top grade, and the distributions by grade were significantly different. At Month 12 the position was much the same, and by Month 18 (see Table) 48 per cent. of the gold series had attained this grade as compared with only 27 per cent. of the controls. 12 months later, this advantage to the gold-treated series still persisted, 51 per cent. being in Grade 1 compared with 29 per cent. of the controls.

Re-grading by Functional Capacity.—By the 18th month of the trial, the percentage of patients in each series who were upgraded or downgraded were as follows:

Gold: Upgraded 58, downgraded 8, no change 34.
Control: Upgraded 27, downgraded 7, no change 66.

Between 18 and 30 months, the percentages were:

Gold: Upgraded 14, downgraded 14, no change 72.
Control: Upgraded 7, downgraded 7, no change 86.

Comparing Month 30 with the initial assessment —33 per cent. of the controls, but 60 per cent. of the gold series—nearly double the proportion—finished in a higher grade than that in which they started:

Gold: Upgraded 60, downgraded 12, no change 28.
Control: Upgraded 33, downgraded 11, no change 56.

In consequence, the distributions of the two groups by grade, were significantly different at Month 30. These proportions, however, relate only to those followed for the complete 30 months, and if it is held that the patients excluded because treatment was changed owing to deterioration (gold 11, control 7) should be added to the number downgraded, then the revised percentages become:

Gold: Upgraded 52, downgraded 23, no change 25.
Control: Upgraded 30, downgraded 18, no change 52.

The distributions were still significantly different at Month 30, the advantage lying with the gold series.

In the event, not all of the patients excluded fell into a lower grading subsequent to their exclusion, probably because of a spontaneous remission or a response to the new treatment rather than because of a response to the gold therapy of the trial.

* For definitions of these grades see previous report.
† Adopted as a convenient summarization of the distributions, although statistically unjustifiable because the grades are not quantitative, but qualitative.

TABLE V

GRADE OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT PERIODICAL ASSESSMENTS, SHOWING PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

(GOLD 77; CONTROL 82)

Month of Assessment	Series	Grade					
		1 = Best	2	3	4	5	"Mean"*
0	Gold	10	52	34	4	—	2·3
	Control	11	60	29	—	—	2·2
18	Gold S	48	38	12	2	—	1·7
	Control	27	52	21	—	—	1·9
30	Gold S	51	32	13	2	1	1·7
	Control	29	50	20	1	—	1·9

* See footnote to Table III for use of term "Mean".
S = Significant difference between the distributions of the two groups.

In order to allow for differences between the two groups as regards the *amount* of upgrading and downgrading which was possible, the actual score was expressed as a percentage of the possible score* over the whole 30 months of the trial. The results (below) confirmed the significant advantage to the gold series as regards functional improvement.

Actual as Percentage of Possible Score

Series	Upgrading	Downgrading
Gold	56	5
	S	
Control ..	30	4

S = Significant difference.

Patient's Own Estimate of Fitness (Table VI)

At each assessment, the patient himself graded his condition as 100, 75, 50, 25, or 1 per cent. fit. During the course of injections the mean grade rose from an initial level of 60 per cent. for both series, to 79 per cent. for the gold series, but to only 72 per cent. for the controls (see previous report). At Month 6 the distributions of the two series by grade showed a significant difference. Thereafter little change in the mean occurred in the gold series, but the controls continued to improve (last column, Table VI) so that at Month 18,† and also at Month 30, there was little difference between the means of the two series, and the distributions were not significantly different.

Regrading by Patient's Estimate.—By Month 18 the percentages of patients who felt better or worse in each series were as follows:

Gold: felt better 62; felt worse 5; no change 33.
Control: felt better 51; felt worse 9; no change 40.

Between Month 18 and Month 30 the proportions were:

Gold: felt better 19; felt worse 23; no change 58.
Control: felt better 11; felt worse 11; no change 78.

Comparing Month 30 with the initial assessment, the results were:

Gold: felt better 64; felt worse 13; no change 23.
Control: felt better 51; felt worse 9; no change 40.

These figures exclude, however, the patients whose treatment was changed because of deterioration (gold 11, control 7) and, if these are added to those who "felt worse", the revised percentages—based on 88 gold and 89 controls—become:

Gold: felt better 56; felt worse 24; no change 20.
Control: felt better 47; felt worse 16; no change 37.

The distributions in these categories are significantly different, but it should be noted that the chief constituent of the difference is the "no change" category—more of the gold series than the controls felt better, but also more of them felt worse.

Expressing the actual score for re-grading as a percentage of the possible score, the only significant differences between the gold and control patients occurred at Month 3 and Month 6 (previous report) and between Months 18 and 30, showing advantage to the gold series at each stage.

Actual as Percentage of Possible Score for Upgrading

Series	Months			
	0-3	3-6	18-30	0-30
Gold	30	37	24	53
Control ..	19	20	11	43

* The method of computation was explained in the previous report.
† *Erratum:* In the previous report the footnote to Table VII (p. 104) should have read "S = Significant difference between the proportions 100 per cent. fit", and *not* "S = Significant difference between the distributions".
In that Table the distributions were significantly different at 6 and 12 months, but not at 18 months.

TABLE VI

PERCENTAGE FITNESS (PATIENT'S OWN ESTIMATE), IN EACH GRADE AT EACH ASSESSMENT
(GOLD 77; CONTROL 82)

Month of Assessment	Series	Fitness (per cent.)					
		100	75	50	25	1	Mean
0	Gold	4	42	45	9	—	60·1
	Control	6	40	44	10	—	60·7
18	Gold	40	39	17	3	1	78·6
	Control	26	49	24	1	—	74·7
30	Gold	40	35	19	4	1	77·3
	Control	28	49	18	5	—	75·0

It will be seen that over the whole period the actual upgrading score attained was 53 per cent. of the possible score in the gold series, and 43 per cent. in the controls, not a significant difference.

Whilst, therefore, the patient's subjective estimates of improvement supported, to some extent, the results of the physicians' objective assessments, they were less conclusive as to the advantage to the gold series after a 30-month follow-up.

Joints Involved, Clinical Assessment

A joint was considered affected if two of three features—swelling, tenderness, and limitation of movement—were present. The 42 joints examined at each assessment comprised proximal, interphalangeal, and metacarpophalangeal joints (20), metatarsophalangeal (10), wrists, elbows, shoulders, hips, knees, and ankles (12).

The record form indicated which of the 42 joints examined were active at each assessment and it was possible, adopting the conventional definitions below, to calculate for each patient, at each successive assessment, the number of joints which became newly affected, quiescent, or re-activated.

A newly affected joint was one recorded at the current assessment as active for the first time during the survey period.

A joint becoming quiescent was one recorded as active at the previous but not at the current assessment.

A re-activated joint was one which was recorded at some earlier assessment (during the trial) as becoming quiescent, but which at the current assessment had again become active.

Mean Number of Joints Active (Tables VII and VIII).—At the outset the mean number of joints affected per patient was nearly the same for both series (gold 17·6, control 18·2). At Month 18 both series showed a reduction, greater in the gold series, so that the means were significantly different (gold 7·7, control 11·9). This difference of 4·2 joints per patient contracted by Month 30 to 1·9 (not significant) because the mean number of affected joints rose slightly in the gold series, and declined in the controls (gold 8·8, control 10·7).

Alternatively (last column of Table VII), it can be said that at Month 18 the average number of joints affected per patient in the gold series fell to 44 per cent. of the initial number and that at Month 30 it rose again to 50 per cent. In the controls it declined to 66 per cent. at Month 18 and declined further to 59 per cent. at Month 30.

TABLE VII

MEAN NUMBER OF JOINTS AFFECTED PER PATIENT

(GOLD 77; CONTROL 82)

Month of Assessment	Mean Number of Joints Affected		Trend (Month 0 = 100 per cent.)	
	Gold	Control	Gold	Control
0	17·6±1·00	18·2±0·98	100	100
18	7·7±0·83 S	11·9±0·99	44	66
30	8·8±0·92	10·7±1·07	50	59

S = Significant difference between the two series.

The extent to which these changes in the mean number of joints affected arose from newly affected joints, those which became quiescent, and those which re-activated is analysed in Table VIII. In the construction of this Table, all the information available from intermediate assessments (Months 3, 6, and 12) was utilized in counting the numbers of new, quiescent, and re-activating joints within the period 0 to 18 months. For example, a joint inactive at Month 0, active at Month 3, inactive at Month 12, and active again at Month 18 was included under all three counts—new, quiescent, and re-activating. Table VIII is to be read as follows:

In the gold series 17·6 joints per patient were active at the outset. Over the first 18 months, the mean number of newly affected joints per patient was 4·3, the mean number which became quiescent was 20·6, and the mean number re-activating was 6·4. As a result the mean number active at Month 18 was 7·7 (*i.e.* 17·6 + 4·3N − 20·6Q + 6·4R). Between Month 18 and Month 30 a mean number of 1·7 new, 2·7 quiescent, and 2·1 re-activating joints was recorded, so that at Month 30 8·8 joints were active per patient (7·7 + 1·7N − 2·7Q + 2·1R).

TABLE VIII

MEAN NUMBER OF JOINTS PER PATIENT BECOMING NEWLY AFFECTED, QUIESCENT, OR RE-ACTIVATED BETWEEN ASSESSMENTS

(GOLD 77; CONTROL 82)

State of Joints	0 to 18 Months		18 to 30 Months	
	Gold	Control	Gold	Control
Active at Start of Period ..	17·6	18·2	7·7 S	11·9
Became Newly Affected ..	+ 4·3	+ 5·6	+1·7	+ 0·8
Became Quiescent	−20·6	−18·9	−2·7 S	− 4·2
Became Re-activated	+ 6·4	+ 7·0	+2·1	+ 2·2
Active at End of Period ..	7·7 S	11·9	8·8	10·7

S = Significant difference between the two series.

It will be noted that, in the first period, fewer joints became newly affected and re-activated, and more became quiescent in the gold series than in the controls, but that in the final period more joints became newly affected and fewer became quiescent in the gold series.

Actual as a Percentage of the Possible Number of Joints Affected (Table IX).—A refinement—allowing for differences between the two treatment series as regards the number of joints which *could* become newly affected, or quiescent, or re-activating—expresses the actual numbers in these categories as percentages of the possible numbers. The formulae used in calculating these indexes are given in the Appendix.

NEWLY AFFECTED JOINTS.—Over the whole 30 months, the percentage of *possible* new joints, *i.e.* those not initially active, which became affected, was similar for the two groups (gold 24·6 per cent., control 27·1 per cent.).

In the two periods, however, the results were different. In the first 18 months the percentage becoming newly affected was significantly lower in the gold series—17·8 per cent. as against 23·6 per cent. in the controls. From the 18th to the 30th month (the possible numbers were here reduced by the number which had already become active in the first period) the proportion was significantly higher in the gold series (8·4 per cent.) than in the controls (4·5 per cent.). The gold-treated series did better in respect of the extension of the arthritis to new joints up to 18 months, but worse thereafter.

QUIESCENT JOINTS.—Joints recorded as inactive at any assessment (Months 1, 3, 6, 12, 18, and 30), but which had been active at the preceding assessment, were counted as quiescent. Some became quiescent more than once during the trial. Over the whole 30 months, in the gold series 83 per cent. of a possible 2,179 became quiescent, as against 75 per cent. of a possible 2,531 in the control series.

This advantage to the gold-treated patients over the whole period, although statistically significant, was not large, and was limited to the first 18 months, in which period 81 per cent. of the possible number became quiescent compared with only 68 per cent. in the control series. In the final period (18 to 30 months), an equal proportion of the "possible" joints became quiescent in both series (35 per cent.) and this contrasts with the previous result (Table VIII), which shows that the mean number of joints becoming quiescent was significantly higher in the control series. This emphasizes the necessity of taking into account the number of joints that *could* become quiescent.

JOINTS WHICH RE-ACTIVATED.—A count of these at each assessment comprised joints which had been recorded as quiescent at an ealier assessment, but which were recorded as becoming active again at the current assessment.

Over the whole 30 months, 41 per cent. of the possible number (see Appendix) became re-activated in the gold series as compared with 49 per cent. in the control series. This statistically significant advantage to the gold group was a feature both of the first 18 months (gold 34 per cent.; control 44 per cent.) and in diminished degree of the second period—18 to 30 months—also (gold 15 per cent., control 18 per cent.).

TABLE IX

NEWLY AFFECTED, QUIESCENT, AND RE-ACTIVATING JOINTS, ACTUAL AS PERCENTAGE OF POSSIBLE NUMBER

(GOLD 77; CONTROL 82)

State of Joints	Series	Period of Assessment (mths)		
		0–18	18–30	Total (0–30)
Newly Affected	Gold	17·8 (1,879) S	8·4 (1,545) S	24·6 (1,879)
	Control	23·6 (1,948)	4·5 (1,488)	27·1 (1,948)
Quiescent	Gold	81·3 (1,963) S	35·6 (592)	82·9 (2,179) S
	Control	68·0 (2,284)	35·4 (979)	75·0 (2,531)
Re-activating	Gold	34·1 (1,436) S	14·9 (1,106) S	41·0 (1,596) S
	Control	43·6 (1,318)	18·3 (977)	48·6 (1,552)

* Significant difference between the two treatment series.

Figures in brackets indicate the "possible" number of joints on which the percentages are based (see Appendix, p. 333). The possible numbers are calculated as follows:

Newly Affected = (0–18) Inactive at start;
(18–30) Inactive at start, less joints newly affected up to Month 18;
(0–30) Inactive at start.

Quiescent = (0–18) Active at start, plus newly affected and re-activating up to Month 12;
(18–30) Active at Month 18;
(0–30) Active at start, plus newly affected and re-activating up to Month 18.

Re-activating = (0–18) Quiescent up to Month 12;
(18–30) Quiescent up to Month 18, less those which re-activated;
(0–30) Quiescent up to Month 18.

Summary of Joints Affected.—In summary, the gold series fared better as regards new joints, quiescent joints, and re-activating joints in the first 18 months. Subsequently, however, the gold patients did no better than the control patients as regards quiescent joints, fared worse as regards newly affected joints, and showed an advantage over the controls only in regard to the re-activated joints.

It is these contrasts that account for the mean number of joints affected per patient being significantly lower in the gold series than in the controls at Month 18, but not at Month 30.

Strength of Grip (Table X)

The strength of the grip of each hand was measured at each assessment in mm. Hg, with an initial bag pressure of 30 mm. maintained for 3 seconds, the hand being held away from the body. The mean of two grips with each hand was recorded.

In the previous report it was shown that for each hand the mean values of the gold and control series were significantly different by Month 6, with advantage to the gold series. This advantage was maintained to the 18th month (Table X), but by the 30th month the mean grip of those treated with gold had fallen considerably, whilst that of the controls was unchanged, so that the small residual advantage to the gold series was no longer statistically significant at Month 30.

TABLE X

MEAN STRENGTH OF GRIP (mm. Hg)
(GOLD 77; CONTROL 82)

Hand	Series	Month of Assessment		
		0	18	30
Right ..	Gold	148±7	180±7S	168±7
	Control	146±7	157±7S	159±7
Left ..	Gold	150±7	180±7S	167±7
	Control	145±7	155±7S	156±7

S = Significant difference between the two series.

Laboratory Investigations

Haemoglobin Concentration (Table XI).—During the first 18 months, the mean haemoglobin level in the gold series increased from 12·3 to 13·0 g. per cent., but in the control group from 12·3 to only 12·5 g. per cent. At Month 18, therefore, the levels of the two series were just significantly different. The earlier analysis indicated that this advantage to the gold-treated series was present as early as the 6th month. By Month 30, however, the haemoglobin concentration had fallen in the gold series, and had risen slightly in the controls, so that at the end of the trial the mean levels were again almost identical.

TABLE XI

MEAN HAEMOGLOBIN CONCENTRATION
(g. per cent. ±S.E.)
(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	12·3±0·19	13·0±0·17S	12·8±0·17
Control	12·3±0·17	12·5±0·18S	12·7±0·18

S = Significant difference between the two series.

Erythrocyte Sedimentation Rate (Table XII).—The results were similar to those for grip and haemoglobin levels. The mean E.S.R. fell in the gold series to a level significantly below that in the control series by Month 6. The advantage was maintained to Month 18, when the mean rates were 27 for the gold series and 33 for the controls, but by Month 30 the mean rate for the gold series had risen again to 32—precisely the same level as that for the controls—and the advantage present in the former from Month 6 to Month 18 had disappeared.

TABLE XII

MEAN ERYTHROCYTE SEDIMENTATION RATE
(mm./hr Westergren)
(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	42±2·4	27±2·3	32±3·0
Control	39±2·3	33±2·3	32±2·4

White Cell Count.—This investigation was not done consistently for every patient at each assessment, and the results are based on the "total" counts of 74 patients in the gold series and 75 controls, and on "polymorph" counts of 61 in each group—not always the same patients at each assessment.

No differences in the mean total or polymorph counts were found at the start, at 18 months, or at 30 months. The total count of the gold series had been significantly lower than that of the controls at Months 1, 3, and 6 (see previous report).

Sheep Cell Agglutination Test (Table XIII).—In order to aggregate the records from the different centres, the titre which each regarded as the minimal positive was taken as 0, successive doubling dilutions above this as +1, +2, +3, etc., and titres below the minimum positive as −1, −2, −3, etc.

Table XIII shows the percentages in the dilution categories for Months 0, 18, and 30, but because the test was not done regularly on many of the patients, particularly at the 18th month, the interpretation of the results is largely speculative.

66 of the 77 gold-treated patients and 73 of the 82 controls were tested at the outset, and the distributions (by dilution groups) were very similar. 70 per cent. of the gold series and 75 per cent. of the controls were positive. By Month 18 the proportion positive in both groups had fallen to 61 per cent., and at Month 30 this proportion was hardly changed (gold 63 per cent., control 65 per cent.).

This apparent similarity, however, of the gold and control series as regards the proportion with positive tests, masks important differences in the *distribution* of the positive results by titre. In the gold series there was a *decrease* in the proportion of high positive titres (titres 4 and over) at Month 18—from 18 to 7 per cent.—and an *increase* in the proportion of low positives. But in the controls there was a *slight increase* in the proportion of high positives and a *decrease* in the proportion of low positives. As a result, the distributions of the gold and control series were almost significantly different at Month 18. Subsequently, the proportion of high positives increased again in the gold series, so that at Month 30 the distributions were again very similar.

It seemed possible that the feature of few high positives in the gold series at Month 18 might be due to the relatively small number tested at this point and to the consequent fortuitous omission of tests in high positive patients. To examine this, the analysis was repeated, using only the 36 patients on gold and the 45 controls for whom there were assessments at all three points (Months 0, 18, and 30). The feature persisted: the proportion of high positives in the gold series fell from 22 per cent. (at Month 0) to 6 per cent. (at Month 18), and then increased to 31 per cent. (at Month 30). In the controls the proportion of high positives increased from 20 per cent. (at Month 0) to 31 per cent. (at Month 18) and to 33 per cent. (at Month 30). As a result there was a significant advantage to those on gold at Month 18 even in this small group who were tested at all three assessments.

Change in S.C.A.T. Titres (Tables XIV and XV, opposite).—For the patients (gold 36, control 45) in whom this test was performed at all three assessments (Months 0, 18, and 30) the change in S.C.A.T. titres is analysed in Table XIV, which is to be read as follows:

Taking the patients who were *Highly Positive Initially* (+4 to +8 dilutions above minimal positive value), there were eight on gold, and nine controls in this high-titre group at the start. At Month 18, the titres of six of the eight on gold had decreased (one became negative), but only one of the nine controls showed a lower titre. At Month 30 all but two (on gold) had reverted to the initial high titre.

The figures for other dilution groups can be interpreted similarly.

Summarizing these changes, the evidence is that in the gold series up to 18 months, the agglutination titres shifted to lower dilutions to a greater extent than in the controls (Table XV, top section).

Table XIII

SHEEP-CELL AGGLUTINATION TEST
Percentage Distributions*

Month of Assessment	Series	S.C.A.T.							No. of Patients Tested†	No. of Patients Not Tested
		Negative			Positive					
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +8	Total		
0	Gold	3	27	30	23	29	18	70	66	11
	Control	8	17	25	26	27	22	75	73	9
18	Gold	6	33	39	26	28	7	61	46	31
	Control	13	26	39	19	17	25	61	54	28
30	Gold	11	26	37	19	19	25	63	53	24
	Control	8	27	35	18	18	29	65	62	20

* The titre regarded as minimal positive at each Centre = 0.

† Numbers on which percentages are based.

TABLE XIV

CHANGE IN S.C.A.T. TITRES FOR PATIENTS TESTED AT MONTHS 0, 18, AND 30

(GOLD 36; CONTROL 45)

S.C.A.T. Dilution Groups* at Start	Series	Total at Start	Dilutions at Month 18					Dilutions at Month 30				
			+4 to +8	+2 to +3	0 to +1	−1 to −2	−3 to −5	+4 to +8	+2 to +3	0 to +1	−1 to −2	−3 to −5
+4 to +8	Gold	8	2	3	2	1	—	6	—	1	—	1
	Control	9	8	1	—	—	—	9	—	—	—	—
+2 to +3	Gold	12	—	5	4	3	—	3	5	1	3	—
	Control	13	5	4	1	2	1	6	2	1	3	1
0 to +1	Gold	8	—	2	1	5	—	1	2	2	2	1
	Control	12	1	2	1	6	2	—	2	4	5	1
−1 to −2	Gold	8	—	—	2	3	3	1	—	1	4	2
	Control	6	—	—	2	2	2	—	1	—	4	1
−3 to −5	Gold	—	—	—	—	—	—	—	—	—	—	—
	Control	5	—	—	3	—	2	—	—	3	—	2
Distribution at End of Each Period	Gold	36	2	10	9	12	3	11	7	5	9	4
	Control	45	14	7	7	10	7	15	5	8	12	5

* Minimal positive at each centre = 0.
Figures in boxes = No change.
Figures to right of boxes = Change to lower dilutions.
Figures to left of boxes = Change to higher dilutions.

TABLE XV

SUMMARY OF THE CHANGE IN THE S.C.A.T. TITRES OF PATIENTS TESTED AT MONTHS 0, 18, AND 30

(GOLD 36; CONTROL 45)

Time of Test	Series	Agglutination Titre			No. of Patients
		Higher	Same	Lower	
Month 18	Gold	4	11	21	36
	Control	13	17	15	45
Between Months 18 and 30	Gold	14	18	4	36
	Control	10	26	9	45
Between Months 0 and 30	Gold	8	17	11	36
	Control	12	21	12	45
Between Months 0 and 30, including Patients not Tested at Month 18	Gold	12	24	11	47
	Control	15	29	13	57

Between 18 and 30 months, a reverse trend was present—more shifted to higher dilutions in the gold than in the control series (Table XV, second section).

When the titres at Month 30 were compared with the initial levels, it was found that about as many patients had changed to higher titres as had changed to lower titres, and this was true of both the gold and control series. It also held when the numbers were increased—as they could be for this last comparison—by the patients tested at Months 0 and 30, but not at Month 18 (Table XV, Sections 3 and 4).

Analgesic Tablets Taken (Table XVI)

At each attendance the number and type of analgesic tablets taken per day were recorded retrospectively. In the few patients taking tablets other than aspirin, the dose was estimated in terms of the aspirin equivalent.*

* See previous report for details.

At the start, both series were taking an average of eight tablets per day. At Month 18 the gold-treated patients had reduced this to five per day, but the controls were practically unchanged. At Month 30, both series were taking an average of six tablets per day.

TABLE XVI

MEAN NUMBER OF ANALGESIC TABLETS TAKEN PER PATIENT

(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	8·0±0·49	5·2±0·49S	6·0±0·55
Control	7·7±0·49	7·4±0·55	6·2±0·53

S = Significant difference between the two series.

Radiological Findings

X-ray films of the hands were available at entry to the trial, and also at Months 18 and 30 for all but two of the gold-treated patients (whose 30-month films were unsatisfactory) and one of the controls (who refused *X*-ray examination at the final assessment). *X*-ray films of the wrists were unassessable in two other patients on gold and one other control. Assessment of radiological progress was therefore restricted to 75 gold-treated patients and 81 controls for hands and to 73 on gold and 80 controls for wrists. The films were read by one observer (Dr. Ifor Pennant Williams), who was unaware to which treatment series each patient belonged.

Comparison at the Start of the Trial (Table XVII).—The metaphalangeal joints, the proximal interphalangeal joints of the fingers, and the interphalangeal joints of the thumbs were examined—a total of twenty joints for each patient. In the gold series, four joints were unassessable (two patients with one joint each, and one with two). In the control group five joints were unassessable (two patients with two each, and one with one).

Table XVII, Section A, shows that the average number of joints per patient initially affected in any way, the average number of joints per patient which were narrowed, and the average number of erosions present for each patient, were similar in the two treatment series at the start of the trial.

The two series differed, however, in regard to the wrists (Table XVII, Section B)—a point noted also in our previous report. A higher proportion of the control patients than those on gold (73 as against 45 per cent.) were graded for the right wrist as "nil or only slightly affected". For the left wrist the comparable proportions were 65 and 49 per cent.—a similar type of difference, but not significant. Taking both wrists together, the higher proportion of controls with neither wrist more than slightly affected still persisted (control 58 per cent., gold 38 per cent.), and there were fewer controls with advanced signs in at least one wrist (control 10 per cent., gold 24 per cent.). This was the only factor examined in the whole survey for which the two groups were not similar initially.

Change in Radiological Signs (Tables XVIII and XIX, opposite).—Progression was assessed by comparing the Month 18 film with the initial film; and the Month 30 film with both the Month 18 film and the initial film. In each of these three comparisons the following particulars were recorded for each patient as regards joints of the hands:

(*a*) The number of joints which had narrowed,
(*b*) The number of new erosions,

TABLE XVII

RADIOLOGICAL COMPARISON OF THE TWO GROUPS AT START OF TRIAL

(A) Initial Radiological Signs in the Joints of the Hands (mean per person)
(GOLD 75; CONTROL 81)

Series	Gold	Control
Joints Affected in Any Way	6·3±0·51	5·9±0·52
Narrowed Joints	2·8±0·39	2·4±0·37
Erosions Present	7·1±0·75	6·8±0·77

(B) Initial Radiological Assessment (per cent.) of Wrists (in four grades)
(GOLD 73; CONTROL 80)

Grade	Left Wrist		Right Wrist		Both Wrists		
	Gold	Control	Gold	Control	Grade*	Gold	Control
Nil or Slight (0)	49	65	45 S	73	0, 0	38 S	58
Moderate (1)	33	26	36	20	0, 1 (or 1, 0)	18	23
Marked (2)	18	9	19	7	1, 1	19	10
					0, 2 (or 2, 0) 1, 2 (or 2, 1)	12	4
					2, 2	12	6

*0, 0 = Nil or slight in both hands; 0, 1 = Nil or slight in one hand, moderate in the other, etc.
S = Significant difference between the two series.

TABLE XVIII

RADIOLOGICAL ASSESSMENT OF PROGRESSION OF RHEUMATOID ARTHRITIS IN HANDS

(GOLD 75; CONTROL 81)

Months			0–18		18–30		0–30	
Series			Gold	Control	Gold	Control	Gold	Control
(1) Assessable Joints		Left	749	806	749	802	749	806
		Right	747	809	746	797	747	809
		Both	1,496	1,615	1,495	1,599	1,496	1,615
Narrowed Joints	(2) Assessable Joints which could Narrow (not initially narrowed)	Left	644	708	600	654	644	708
		Right	642	715	595	662	642	715
		Both	1,286	1,423	1,195	1,316	1,286	1,423
	(3) Joints which did Narrow	Left	44	54	63	81	105	123
		Right	47	53	67	82	120	132
		Both	91	107	130	163	225	255
	(4) Actual Joints which Narrowed as Percentage of Possible Number ((3) as percentage of (2))	Left	6·8	7·6	10·5	12·4	16·3	17·4
		Right	7·3	7·4	11·3	12·4	18·7	18·5
		Both	7·1	7·5	10·9	12·4	17·5	17·9
Erosions	(5) New Erosions which Developed	Left	115	179	97	110	184	273
		Right	135	157	86	114	206	277
		Both	250	336	183	224	390	550
	(6) New Erosions per Assessable Joint ((5) ÷ (1))	Left	0·15±0·02	0·22±0·03	0·13±0·03	0·14±0·02	0·25±0·04	0·34±0·04
		Right	0·18±0·03	0·19±0·03	0·12±0·02	0·14±0·02	0·27±0·04	0·34±0·04
		Both	0·17±0·02	0·21±0·02	0·12±0·02	0·14±0·02	0·26±0·04	0·34±0·04
	(7) Extension of Old Erosions	Left	47	49	49	69	50	56
		Right	69	75	73	91	81	99
		Both	116	124	122	160	131	155
	(8) Extensions per Assessable Joint ((7) ÷ (1))	Left	0·06±0·01	0·06±0·01	0·07±0·01	0·09±0·02	0·07±0·01	0·07±0·01
		Right	0·09±0·02	0·09±0·01	0·10±0·02	0·11±0·02	0·11±0·02	0·12±0·01
		Both	0·08±0·01	0·08±0·01	0·08±0·02	0·10±0·01	0·09±0·02	0·09±0·01

Note: Items (6) and (8) were computed in two ways:
(*a*) by relating, *e.g.* the total new erosions for all patients to the total assessable joints;
(*b*) individually for each patient; and calculating the mean ± S.E. of the resulting series.
The two methods gave almost identical means.

TABLE XIX

PERCENTAGE RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN THE WRISTS

(GOLD 73; CONTROL 80)

Months	Wrist		Left		Right		Both		
	Series		Gold	Control	Gold	Control	Grade*	Gold	Control
0–30	Progression Grade	Nil or Slight 0	36	34	32	34	0, 0	22	23
		Moderate 1	25	29	37	33	0, 1	15	16
		Marked 2	23	23	16	23	1, 1	15	16
		Very marked 3	16	15	15	11	0, 2+	8	6
							1, 2+	16	13
							2+, 2+	23	26
		Total	100	101	100	101	—	99	100
0–18		2 and 3 Combined	10	21	11	16	2+ in one or both hands	14	28
18–30		2 and 3 Combined	11	14	15	12	2+ in one or both hands	17	18

* 0, 0 = Nil or slight in both hands; 0, 1 = Nil or slight in one hand, moderate in the other, etc.

(*c*) The number of extensions of erosions which were visible in the earlier of the two films.

The summation of these for all patients in each treatment series is shown in Table XVIII (Rows 3, 5, and 7). Discrepancies between the counts for the whole 30-month period and the summation of the 0 to 18- and the 18 to 30-month periods arise from "observer error", whereby a joint thought to be narrowed at Month 18 might look "normal" at Month 30, or an erosion extended at Month 18 might not be visible at Month 30, either because it had become unrecognizable or because of a slight rotation of the finger. Also, three erosions at Month 18 may coalesce to give one large one at

Month 30. It is therefore better to regard the three readings (periods) as separate experiments.

Three indices of progression of the disease in the patients were derived from these counts—Rows 4, 6, and 8 of Table XVIII. They show that, measured radiologically, there were no statistically significant differences between the gold series and the controls as regards joint narrowing, the development of new erosions, or the extension of old erosions throughout the whole trial or in the earlier or later part of it. Nevertheless, the *consistency* of the slightly higher mean values in the control group as regards joint narrowing and new erosions in either hand is perhaps more important than any numerical test of significance.

Progression in the wrist in each period was assessed radiologically in four grades (Table XIX), with the following rough guides:

0	*Nil or Slight:*	No change, or small erosion and/or small area of cartilage loss, *i.e.* joint narrowing.
1	*Moderate:*	Two to five erosions and/or narrowing involving two or three carpal joints.
2	*Marked:*	Four to eight erosions. Narrowing very obvious.
3	*Very marked:*	Virtually every joint in the wrist showing narrowing and erosions.

Here again no differences between the two treatment groups were manifested in either period of the trial as regards the percentages in the four progression categories.

In view of this, for economy in space, only the percentages showing marked and very marked progression (Grades 2 and 3 combined) are tabulated for the first and second periods of the trial.

There is a suggestion in these figures that in the first 18 months, a higher percentage of the control group showed moderate or marked progression (gold 14 per cent., control 28 per cent.), but the difference is not statistically significant.

To obtain some general measure of the progression in the hands a scoring system was used by which a joint which narrowed scored one point, a new erosion scored two points, and an extension of an old erosion scored one point. The actual scores were then expressed as percentages of the possible scores* (Table XX). No significant differences were seen, but again the consistency with which the index was slightly in favour of the gold-treated series is very suggestive. The actual score as a percentage of the possible score for radiological progression in both hands together over the complete 30 months of the trial was 8·6 per cent. for the gold series as compared with 10·5 per cent. for the controls, and the advantage to the gold-treated patients was of this order in each hand and for each period of the trial.

Patients Given a Second Course

As explained earlier (see p. 315), sixteen of the gold-treated patients and eighteen controls received a second course of injections after the 18-month assessment. For brevity, the one-course group will be referred to as Group A, and the two-course group as Group B.

A review of the requests for second courses revealed that where a reason was stated, the most

* A detailed explanation of the computation of these possible scores was given in the previous report and was adopted unchanged for all three periods examined in Table XX.

TABLE XX

RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN HANDS ALONE (TOTAL FOR ALL PATIENTS)
(GOLD 75; CONTROL 81)

Months	Series		Gold			Control		
	Hand		Left	Right	Both	Left	Right	Both
0–18	Score	Actual	321	386	707	461	442	903
		Possible	6,636	6,618	13,254	7,156	7,187	14,343
		Actual as Percentage of Possible	4·84	5·83	5·33	6·44	6·15	6·30
18–30	Score	Actual	306	312	618	370	401	771
		Possible	6,592	6,563	13,155	7,070	7,038	14,108
		Actual as Percentage of Possible	4·64	4·75	4·70	5·23	5·70	5·46
0–30	Score	Actual	523	613	1,136	725	785	1,510
		Possible	6,636	6,618	13,254	7,156	7,187	14,343
		Actual as Percentage of Possible	7·88	9·26	8·57	10·13	10·92	10·53

* For tests of significance, this index was calculated for each patient and the means and standard errors computed from the resulting series. The means thus obtained differed only slightly from the overall values shown in this Table.

usual one was deterioration in the patient's condition. There were, therefore, three main points for study: to determine whether the two-course patients were a select group in that their progress had been unsatisfactory; to note how their progress between the 18th and 30th months compared with that of those who did not receive a second course; and to decide whether, if the two-course patients *were* select sub-groups, their exclusion would have modified the conclusions reached from the earlier analysis.

Both in the gold-treated and in the control series, Groups A and B were similar at the start of the trial as regards sex, age, duration of symptoms, and type of onset. Group B in each series contained fewer males but, on the small numbers involved, the sex proportions were not significantly different. Also, as regards most of the factors used in assessing progress, these sub-groups were not significantly different at the outset except, possibly, in respect of grip.

Functional Capacity (Physician's Estimate) (Table XXI)

The distributions by functional grade of patients in Groups A and B were not dissimilar at the start of the trial. By Month 18, however, there was a smaller percentage of Group B (6 as against 59 per cent.) in the best grade, and higher percentages of Group B in the other grades. This was true of both series, and implies that, by this index, patients subsequently given a second course were those who had fared relatively badly up to Month 18. (This does not mean, of course, that *all* who did badly received a second course, nor that *all* who received a second course *had* done badly.)

That the Group B patients were a select group who did not do so well up to Month 18, was confirmed by the percentages upgraded and downgraded between Months 0 and 18:

Gold:

A—upgraded 64; downgraded 5; no change 31

B—upgraded 38; downgraded 19; no change 43

Control:

A—upgraded 34; downgraded 5; no change 61

B—upgraded nil; downgraded 17; no change 83

Between Month 18 and Month 30 (there were no interim assessments) no group showed much change in the percentage distribution by functional grading (Table XXI), but the actual score for *downgrading* as a percentage of the possible score was significantly higher for Group B than for Group A in the gold series (12 as against 4 per cent. of the possible score), indicating that, despite their additional course of gold, their condition deteriorated. No corresponding significant difference was found in the control series.

Comparing the gold and control patients who had only one course (Group A), the advantage to the gold group at Month 18 was maintained at Month 30: 61 per cent. of the gold series, but only 36 per cent. of the controls, were in the highest grade (Table XXI), and this is in accordance with the conclusion reached earlier, based on Groups

TABLE XXI

GRADE OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) OF GROUPS A AND B, PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

Series	Month of Assessment	Group	Grade											
			1 = Best		2		3		4		5		"Mean"*	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gold	0	A	7	11	34	56	19	31	1	2		—	61	2·2
		B	1	6	6	38	7	44	2	12		—	16	2·6
	18	A	36	59	20	33	5	8		—		—	61	1·5
		B	1	6	9	56	4	25	2	12		—	16	2·4
	30	A	37	61	17	28	7	11		—		—	61	1·5
		B	2	12	8	50	3	19	2	12	1	6	16	2·5
Control	0	A	8	12	37	58	19	30		—		—	64	2·2
		B	1	6	12	67	5	28		—		—	18	2·2
	18	A	21	33	33	51	10	16		—		—	64	1·8
		B	1	6	10	56	7	39		—		—	18	2·3
	30	A	23	36	31	48	10	16		—		—	64	1·8
		B	1	6	10	56	6	33	1	6		—	18	2·4

* See footnote to Table III for use of the term "Mean".
A = One course.
B = Two courses.

A and B combined. In other words, the exclusion of the B Groups from the earlier analysis would not have modified the conclusions regarding the advantage of those treated by gold.

Furthermore, the fact that those who had second courses of gold did no better subsequently than those who had second courses of the control injections suggests that the former were resistant to gold therapy.

Patient's Estimate of Fitness (Table XXII)

A very similar picture is given by the patients' subjective estimates of fitness. In Group A of the gold series, the percentage feeling 100 per cent. fit increased from 5 to 49 per cent. between Months 0 and 18, but in Group B of the gold series it rose from nil to only 6 per cent. (one out of the sixteen patients). At Month 18 the distributions were significantly different. The controls gave a similar picture.

Further analysis showed that the percentages grading themselves at Month 18 as "more fit" or "less fit" than at the start of the trial were as follows:

Gold:
A—more fit 69; less fit 3; no change 28
B—more fit 38; less fit 12; no change 50
Controls:
A—more fit 56; less fit 8; no change 36
B—more fit 33; less fit 11; no change 56

By this index also, therefore, Group B had improved less than Group A up to the time of receiving the second course.

Subsequently, little difference in the progress of Groups A and B on gold could be distinguished. Certainly the mean grade of the former was slightly reduced (83 to 80 per cent. fit), whilst the mean grade of the latter went up (63 to 67 per cent. fit), but on the small numbers involved the change in the distributions was not greater than could arise by chance. Similar remarks apply to the A and B sub-groups in the control series.

Taking Group A only, over the whole 30 months of the trial, the actual score for upgrading as a percentage of the possible score was 58 per cent. in the gold series as against 49 per cent. in the control series—a non-significant difference similar to that found in the general analyses based on Groups A and B combined. Nor could any real difference be found between the progress of those who had two courses of gold and those who had two courses of control treatment.

Other Criteria

The results of comparing Groups A and B with regard to other criteria (joints affected; new, quiescent, and re-activated joints; grip; haemoglobin concentration; erythrocyte sedimentation rate; sheep cell agglutination titres; and analgesic tablets) were all in conformity with those given by Functional Capacity and Patient's Estimate of Fitness (above).

Space does not permit the presentation of these tabulations;* it will suffice to conclude with those relating to the radiological assessment.

* The tabulations are available if required.

TABLE XXII

PERCENTAGE FITNESS (PATIENT'S OWN ESTIMATE) OF GROUPS A AND B IN EACH GRADE AT EACH ASSESSMENT

Series	Month of Assessment	Group	Fitness (per cent.)											
			100		75		50		25		1		"Mean"*	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gold	0	A	3	5	26	43	27	44	5	8	—		61	61·1
		B	—		6	38	8	50	2	12	—		16	56·3
	18	A_S	30	49	22	36	7	11	2	3	—		61	82·8
		B^S	1	6	8	50	6	38	—		1	6	16	62·6
	30	A	28	46	19	31	12	20	2	3	—		61	79·9
		B	3	19	8	50	3	19	1	6	1	6	16	67·3
Control	0	A	4	6	25	39	28	44	7	11	—		64	60·2
		B	1	6	8	44	8	44	1	6	—		18	62·5
	18	A	20	31	29	45	14	22	1	2	—		64	76·6
		B	1	6	11	61	6	33	—		—		18	68·1
	30	A_S	22	34	31	48	7	11	4	6	—		64	77·7
		B^S	1	6	9	50	8	44	—		—		18	65·3

* See footnote to Table III for use of the term "Mean".
S = Significant difference between the distributions of A and B.
A = One course.
B = Two courses.

Radiological Progression (Tables XXIII and XXIV)

When assessed radiologically, Groups A and B were generally similar at the start of the trial as regards the mean number of joints per person affected, the mean number of narrowed joints per person, and the number of erosions present (Table XXIII). In the control series Group B had significantly *fewer* erosions present initially than Group A. Grading of the wrists (not shown in the Tables) was similar for Groups A and B in each series.

TABLE XXIII

RADIOLOGICAL COMPARISON OF GROUPS A AND B AT START OF TRIAL
(mean number of joints affected per person)

Initial Radiological Signs in Joints of the Hands *	Group	Series	
		Gold	Control
Affected in Any Way ..	A	6·1±0·58	6·5±0·62
	B	7·2±1·03	4·1±0·72
Narrowed	A	2·8±0·40	2·6±0·45
	B	3·0±1·14	1·7±0·51
Erosions Present	A	7·1±0·89	7·5±0·94 S
	B	7·1±1·14	4·3±0·84 S

S = Significant difference between the groups.
A = One course.
B = Two courses.

During the first 18 months, the number of joints which narrowed (as a percentage of the number which could narrow) was significantly higher in Group B than in Group A in the gold series, but this did not apply in the control series. The same was true for the 18 to 30-month period, so that over the whole trial 24 per cent. of hand joints of the two-course gold patients narrowed, as against only 16 per cent. of the one-course gold patients (Table XXIV(*i*)). No difference was found between Groups A and B in the control series.

No significant differences appeared between Groups A and B at either Month 18 or Month 30 as regards the number of new erosions or extensions of old erosions. The separate data for each hand have therefore been omitted (Table XXIV(*ii*) and (*iii*)).

Although at Month 18 a higher proportion of the wrists in Group B showed marked or very marked progression than those in Group A, the differences were not significant on the small numbers involved and had disappeared entirely at Month 30.*

Thus the radiological evidence based on joint narrowing in the hands and on the progression of the disease in the wrists supports the conclusion reached from the clinical assessments that Group B fared relatively poorly up to receiving their second course, and that they did no better after their second course than Group A. Furthermore, a radiological comparison of the gold and control series based on Group A patients only in no way modifies the conclusions drawn from the comparison of Groups A and B combined (p. 327 and Table XVIII), nor was there any evidence that those who had second courses of gold therapy showed more or less radiological progression than those who received a second course of control therapy.

Summary of Second Courses

The comparison of those who had a second course of treatment (Group B) with those who did not (Group A) showed that up to the time of receiving a second course, Group B had improved to a lesser

* The tabulations are available if required.

TABLE XXIV

RADIOLOGICAL PROGRESSION IN JOINTS OF THE HANDS IN GROUPS A AND B

Progression Assessed	Months	Gold						Control					
		Left		Right		Both		Left		Right		Both	
		A	B	A	B	A	B	A	B	A	B	A	B
(*i*) Joints which Narrowed (Percentage of those which could Narrow	0–18	6 S	9	6 S	13	6 S	11	9	5	8	6	8	5
	18–30	9 S	18	11	14	10 S	16	12	15	11	16	11	16
	0–30	15	22	17 S	26	16 S	24	17	18	18	20	18	19
(*ii*) Mean Number of New Erosions (per Assessable Joint)	0–18					0·17±0·03	0·16±0·04					0·20±0·02	0·24±0·07
	18–30					0·11±0·03	0·19±0·05					0·13±0·02	0·17±0·03
	0–30					0·24±0·04	0·35±0·08					0·33±0·04	0·39±0·07
(*iii*) Mean Number of Extensions of Old Erosions (per Assessable Joint)	0–18					0·07±0·01	0·10±0·03					0·08±0·01	0·06±0·02
	18–30					0·08±0·02	0·07±0·02					0·10±0·02	0·11±0·03
	0–30					0·09±0·02	0·07±0·02					0·10±0·02	0·08±0·02

S = Significant difference between the groups.
A = One course.
B = Two courses.

degree. Despite the very small numbers in Group B, significant differences were found in the patient's own estimate of physical well-being, the number of joints newly affected and becoming quiescent, and changes in strength of grip and in erythrocyte sedimentation rate, and frequency of joint narrowing measured radiologically. In most of the other assessments, differences not large enough to reach statistical significance, but all tending the same way, were apparent—showing Group B at a relative disadvantage at the time of receiving the second course.

After receiving the second course Group B remained at a disadvantage: the mean grade of functional capacity fell, whilst that of Group A remained stationary; more joints became newly affected; strength of grip declined more; and a larger proportion of joints narrowed.

Thus the patients given a second course comprised a select sub-group which fared relatively badly during the first 18 months, and did no better after receiving a repeat course.

Furthermore, those who had a second course of gold subsequently did no better than those who had a second course of control therapy, whereas those who did well on a single course of gold had a distinct advantage over the control group.

Discussion

Initially 99 patients were given a 5-month course of twenty weekly gold injections and 100 subjects received control injections; 77 of the former and 82 of the latter were followed for 30 months, 2 full years from the end of the 5-month period of therapy. At the start of the trial the only difference noted between the two series was in regard to radiological assessment of the wrists, which were affected to a lesser degree in the control series. According to the physician's estimate of functional capacity, and analysed in various ways, the results clearly demonstrate an advantage to the gold-treated patients from Month 6 right through to the end of the trial at Month 30. The patient's own estimate of fitness supported the physician's estimate, but was less conclusive, little advantage showing to the gold-treated patients by Month 30. In the first 18 months the gold-treated patients showed fewer newly affected joints than the controls, fewer joints re-activating, and a larger number becoming quiescent; after Month 18 some of this advantage disappeared as more joints were newly affected in the gold series than in the control series from Month 18 to Month 30. Similarly, the haemoglobin concentration, erythrocyte sedimentation rate, and daily consumption of analgesic tablets, were significantly better in the gold series from Month 6 to Month 18 and thereafter deteriorated, so that by Month 30 little, if any, advantage remained. The sheep cell agglutination titres up to Month 18 shifted in the gold-treated series to lower dilutions than in the control series, but from Month 18 to Month 30 a reverse trend was apparent, so that over the whole trial as many titres rose as fell in both gold and control series. As regards radiological findings, no significant differences were seen between the gold and control series in joint narrowing, development of new erosions, or extension of previous erosions, in either period of the trial. Where small differences occurred, although statistically not significant, they were consistently in favour of the gold series.

To sum up, in general the evidence is that, by most of the indices used, the gold-treated patients fared better than the controls from the 3rd to the 6th month up to Month 12, and that this advantage was on the whole maintained up to Month 18, *i.e.* one full year after the completion of the 5-months' course of treatment; after this period the gold-treated patients deteriorated to an appreciable extent, though they retained some small advantage over the controls in regard to some criteria at Month 30.

When the trial was first organized it was left to the individual physician to give a second course of injections if he considered such a course to be indicated, both physician and patient remaining unaware which treatment was being given. Sixteen gold-treated patients and eighteen controls received second (repeat) courses. The analysis has shown that these patients, both gold-treated and controls, comprised a select sub-group who did badly on both courses in both groups. This appears to confirm the impression long held by many clinicians that, if one full course of gold gives little or no benefit, a second course is unlikely to give better results. Additional weight is given to this when it is noted that those who received a second course of gold did no better subsequently than those who received a second course of control injections, whereas those who had only one course of gold still showed some advantage at Month 30 over the controls who had received only one course.

Summary and Conclusions

(1) 159 out-patients aged 20 to 64 years, with active rheumatoid arthritis of 1 to 5 years' duration, who had received gold salts in a 5-month course of

twenty weekly injections, were followed for a total of 30 months from the start of treatment. 77 received weekly injections of 50 mg. sodium aurothiomalate (Myocrysin) to a total dosage of 1 g. (gold series), and 82 received 0·5 μg. weekly of the same substance to a total dosage of 0·01 mg. (control series).

(2) Considerable improvement by all criteria except radiological examination was seen from Month 3 (halfway through the course of injections) to Month 18 (one year after completion of the course). Thereafter, a reverse trend was noted, so that by Month 30 most of the advantage seen in the gold-treated series at Month 18 had disappeared, though by some criteria the gold-treated series still remained significantly better than the control series, albeit by only a slender margin.

(3) Second courses of injections were given to sixteen gold-treated patients and eighteen controls. The main reason for giving a second course was failure to respond satisfactorily to the first. Analysis of the assessments of these patients confirmed that they formed relatively "bad" groups up to the time of receiving the second course, and that subsequently they did no better. In addition, the sixteen who received two courses of gold did no better than the eighteen who received two courses of control injections.

Our thanks are due to all participants in the various centres for their close co-operation, to Miss K. Davies and the staff of the Department of Medical Statistics in the Welsh National School of Medicine for their invaluable assistance, and also to Messrs. May and Baker for generous supplies of Myocrisin (sodium aurothiomalate) used in both series of cases throughout the trial.

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APPENDIX

Newly Affected, Quiescent, and Re-activating Joints

Let i = Months of assessment 0, 1, 3, 6, 12, 18, 30, and for any group of patients;
T_i = Total number of joints examined (generally 42);
A_i = Joints active at assessment i } $(A+I=T)$
I_i = Joints inactive at assessment i }
N_i = Joints becoming active for the first time in the trial at assessment i
Q_i = Joints becoming quiescent at assessment i
R_i = Joints becoming reactive at assessment i
Σ = Summation for all patients in a treatment group.

e.g. $\Sigma\overset{18}{\underset{1}{N}}$ = Total number of newly affected joints recorded by all patients at Months 1, 3, 6, 12, and 18, whilst

ΣI_0 = Number of joints recorded as inactive at Month 0 (start of trial) by all patients.

Then the following formulae give actual numbers as a percentage of the possible numbers:

Newly Affected Joints as Percentage of Possible Number

$$0 - 18 \text{ months} = 100\ \Sigma\overset{18}{\underset{1}{N}} \Big/ \Sigma I_0$$

$$18 - 30 \text{ months} = 100\ \Sigma N_{30} \Big/ \left(\Sigma I_0 - \Sigma\overset{18}{\underset{1}{N}}\right)$$

$$0 - 30 \text{ months} = 100\ \Sigma\overset{30}{\underset{1}{N}} \Big/ \Sigma I_0$$

Joints becoming Quiescent as Percentage of Possible Number

$$0 - 18 \text{ months} = \frac{100\left(\Sigma\overset{18}{\underset{1}{Q}}\right)}{\Sigma A_0 + \Sigma\overset{12}{\underset{1}{N}} + \Sigma\overset{12}{\underset{3}{R}}}$$

$$18 - 30 \text{ months} = 100\ \Sigma Q_{30} / \Sigma A_{18}$$

$$0 - 30 \text{ months} = \frac{100\ \Sigma\overset{30}{\underset{1}{Q}}}{\Sigma A_0 + \Sigma\overset{18}{\underset{1}{N}} + \Sigma\overset{18}{\underset{3}{R}}}$$

Re-activating Joints as Percentage of Possible Number

$$0 - 18 \text{ months} = 100\ \Sigma\overset{18}{\underset{3}{R}} \Big/ \Sigma\overset{12}{\underset{1}{Q}}$$

$$18 - 30 \text{ months} = 100\ \Sigma R_{30} \Big/ \Sigma\overset{18}{\underset{1}{Q}} - \Sigma\overset{18}{\underset{3}{R}}$$

$$0 - 30 \text{ months} = 100\ \Sigma\overset{30}{\underset{3}{R}} \Big/ \Sigma\overset{18}{\underset{1}{Q}}$$

Chrysothérapie de l'arthrite rhumatismale. Rapport final d'un essai contrôlé, multicentral

Résumé et Conclusions

(1) Des malades externes, au nombre de 159, âgés de 20 à 64 ans, atteints d'arthrite rhumatismale évolutive pendant 1 à 5 ans, qui avaient reçu une série d'injections hebdomadaires de sels d'or pendant 5 mois, furent surveillés pendant 30 mois dès le commencement du traitement. Parmi eux, 77 reçurent des injections hebdomadaires de 50 mg. d'aurothiomalate de soude (Myocrisin) atteignant une dose totale de 1 gramme (série traitée) et 82 malades reçurent 0,005 mg. hebdomadaires de la même substance, atteignant une dose totale de 0,01 mg. (série témoin).

(2) Une amélioration considérable selon tous les critères, sauf un examen radiologique, fut observée dès le troisième mois (après la moitié des injections) jusq'au 18-ème mois (un an après la fin des injections). Après cela on nota une tendance opposée, de manière que vers le 30-ème mois, la plupart des avantages observés dans la sèrie traitée à l'or s'était évanouie. Selon certains critères, toutefois, la série traitée se portait significativement mieux que la série témoin, quoique la marge entre les deux était très petite.

(3) Une deuxième série d'injections fut administrée à 16 malades ayant été traités par des sels d'or et à 18 témoins. La raison principale de la deuxième série fut la réponse peu satisfaisante à la première. L'analyse des évaluations de ces malades confirme qu'ils formaient des groupes relativement "mauvais" justqu'au moment de recevoir la deuxième série et qu'après cela ils ne se sont pas améliorés. De plus, les 16 qui avaient reçu deux séries d'injections d'or n'en ont pas profité plus que les 18 qui avaient reçu deux séries d'injections témoins.

Crisoterapia en la artritis reumatoide. Informe final sobre una investigación controlada multicentral

Sumario y Conclusiones

(1) Ciento cincuenta y nueve enfermos externos, de edad de 20 a 64 años, con artritis reumatoide evolutiva de 1 a 5 años de duración, recibieron una serie de inyecciones semanales de sales de oro durante 5 meses y fueron seguidos durante 30 meses desde el comienzo del tratamiento. Entre estos, 77 recibieron inyecciones semanales de 50 mg. de aurotiomalato de sodio (Myocrisin) con una dosis total de 1 gramo (serie tratada) y 82 enfermos recibieron 0,005 mg. semanales del mismo producto con una dosis total de 0,01 mg. (serie de control).

(2) Una mejoría considerable según todos los criterios, salvo un examen radiológico, fué observada desde el tercer mes (en medio de las inyecciones) hasta el diecioctavo mes (un año después del fin de las inyecciones). A continuación se notó una tendencia opuesta, de modo que hacia el treinteno mes la mayoría de las ventajas observadas en la serie tratada con oro desapareció. Según ciertos criterios, sin embargo, la serie tratada con oro andó significativamente mejor que la serie testiga, aunque el margen entre los grupos fué muy pequeño.

(3) Una segunda serie de inyecciones fué administrada a 16 enfermos tratados con oro anteriormente y a 18 testigos. La razón principal de la segunda serie fué la respuesta terapéutica poco satisfactoria a la primera. Un análisis de valoraciones de estos enfermos confirma el hecho de que se trata aquí de grupos que fueron relativamente "malos" antes de recibir la segunda serie y que cambiaron poco después. Además, los 16 que recibieron dos series de inyecciones de oro no se hallaron mejor que los 18 que recibieron dos series de inyecciones testigas.

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RELATION OF TOXIC REACTIONS IN GOLD THERAPY TO IMPROVEMENT IN RHEUMATOID ARTHRITIS

A REPORT

BY

THE RESEARCH SUB-COMMITTEE* OF THE EMPIRE RHEUMATISM COUNCIL

Introduction

It is a common belief that those patients who develop toxic reactions during gold therapy enjoy some measure of remission of their rheumatoid arthritis more frequently as a consequence. Confirmation of this belief has been sought in the records of the Gold Trial recorded on p. 315 of this issue of the *Annals of the Rheumatic Diseases*.

Data and Method

The problem posed was whether the condition of patients with rheumatoid arthritis who developed toxic symptoms during a 5-month course of gold therapy—"the toxic group"—improved more (or less) than those who remained free from such symptoms—"the non-toxic group".

In the preceding report (see p. 315 above) it was shown that 35 of a series of 99 patients treated with 1 g. gold, and 16 of a series of 100 patients treated with 0·01 mg. gold, hereinafter referred to as the controls, experienced at least one toxic reaction. With but one exception (thrombocytopenic purpura in the 12th month), all the reactions occurred during the period in which the injections were given, *i.e.* the first 5 months of the trial.

77 of the gold series (31 toxic, 46 non-toxic) and 82 of the controls (12 toxic, 70 non-toxic) were followed for 30 months from the start of the trial, and this supplementary report compares the progress during this period of the toxic and non-toxic sub-groups of the gold and control series.

The toxic groups were sub-divided into "severe" and "less severe", the former comprising patients with dermatitis (gold 18, controls 6) and purpura (gold 2, controls 1).

This classification of the gold and control series may be summarized as follows:

Series				Gold		Control	
Group	Toxic	Severe	Dermatitis	18	20	6	7
			Purpura	2		1	
		Less Severe		11	31	5	12
	Non-Toxic			46		70	
	Total			77		82	

Table I (overleaf) shows that at the start of the trial the toxic and non-toxic groups did not differ materially as regards sex, age, duration of symptoms, or type of onset of disease. As will appear, they were also similar initially as regards all the indices of assessment.

Since, by most of the indices, the advantage to the gold series was at its peak at the 12-month assessment (*i.e.* 6 months after the completion of the injections), one would expect that any difference between the toxic and non-toxic groups would be most evident at this point, at least in the gold-treated patients.

Attention was therefore concentrated mainly on a comparison of the toxic and non-toxic groups at the 12-month assessment, although for most of the indices comparison was also made at Month 18 and Month 30.

Results

Functional Capacity (Physician's Estimate) (Table II, overleaf)

The distributions of patients in the five grades showed no significant differences between the toxic and non-toxic groups, or between the severe and less severe toxic groups, either at Month 0 or at Month 12.

* For particulars of membership of this sub-committee, see p. 315.

TABLE I

COMPARISON OF THE TOXIC AND NON-TOXIC GROUPS AT THE START OF THE TRIAL

Factors Compared		Series			
		Gold		Controls	
		Toxic	Non-Toxic	Toxic	Non-Toxic
No. of Patients		31	46	12	70
No. of Males		11 (35%)	11 (24%)	2 (17%)	21 (30%)
Age (yrs) (Mean ± S.E.)		49·9±1·67	46·5±1·27	45·9±3·20	47·9±1·14
Duration of Symptoms (yrs)	1 to 3	20 (65%)	29 (63%)	8 (67%)	48 (69%)
	3 to 5	11 (35%)	17 (37%)	4 (33%)	22 (31%)
Type of Onset	Acute	11 (35%)	16 (35%)	4 (33%)	17 (24%)
	Non-acute	20 (65%)	29 (65%)	8 (67%)	53 (76%)
	Not Known	—	1	—	—

The percentages in the two best grades, taken together because of the small number of cases involved, are shown in Table II. In the gold series, at the start, 68 per cent. of the toxic, but only 59 per cent. of the non-toxic group were in these grades at the initial assessment. By Month 12, the percentages were equal (87 per cent.), so that a higher proportion of the non-toxic cases had moved into them. At Month 18, there was a slight but non-significant advantage to the non-toxic group, and at Month 30, no difference. In the control series, the seven patients in the severe toxic group did relatively badly.

TABLE II

PERCENTAGE OF PATIENTS IN THE HIGHEST FUNCTIONAL CAPACITY GRADES (1 AND 2) IN THE TOXIC AND NON-TOXIC GROUPS

Series	Group		No. of Patients	Months from Start of Trial			
				0	12	18	30
Gold	Non-Toxic		46	59	87	89	83
	Toxic	Total	31	68	87	81	84
		Severe	20	75	95	90	80
		Less Severe	11	55	73	64	91
Control	Non-Toxic		70	67	83	79	77
	Toxic	Total	12	92	75	75	75
		Severe	7	86	57	57	57
		Less Severe	5	100	100	100	100

Patient's Estimate of Fitness (Tables III and IV)

These tabulations suggest that patients who developed toxicity on gold were on the average slightly more "fit" at the outset, but the differences were not significant. In the controls this suggestion did not hold good.

At Month 12, the differences in the mean grades were less pronounced (Table III) and a higher proportion of the non-toxic group had become "75 per cent. or more fit" (Table IV). Indeed, in the gold series, there were 44 per cent. more at this level of fitness in the non-toxic group at Month 12 than at Month 0, as against 29 per cent. more in the toxic group.

Within the toxic group the figures suggest that those with severe symptoms did slightly better than those with less severe symptoms.

At 30 months, only 71 per cent. of the toxic group on gold felt "75 per cent. or more fit" as

TABLE III

MEAN GRADES OF PATIENT'S ESTIMATE OF FITNESS IN THE TOXIC AND NON-TOXIC GROUPS

Series	Group		No. of Patients	Mean Grade (as percentage of complete fitness)	
				Month 0	Month 12
Gold	Non-Toxic		46	57	75
	Toxic	Total	31	65	73
		Severe	20	67	81
		Less Severe	11	61	63
Control	Non-Toxic		70	61	71
	Toxic	Total	12	58	70
		Severe	7	59	65
		Less Severe	5	58	85

TABLE IV

PERCENTAGE OF PATIENTS WHO FELT "75 PER CENT. OR MORE FIT" IN THE TOXIC AND NON-TOXIC GROUPS

Series	Group		No. of Patients	Months from Start of Trial			
				0	12	18	30
Gold	Non-Toxic		46	41	85	76	78
	Toxic	Total	31	52	81	81	71
		Severe	20	60	90	95	70
		Less Severe	11	36	64	55	73
Control	Non-Toxic		70	49	79	71	76
	Toxic	Total	12	33	75	75	83
		Severe	7	27	71	71	86
		Less Severe	5	40	80	80	80

against 78 per cent. of the non-toxic group on gold, and there was no difference between the severe and less severe sub-groups in this respect at this final point. In the control series these slight differences were reversed.

Joints Affected (Table V)

At Month 0 there was no real difference between the toxic and non-toxic groups, but by Month 12 the non-toxic group showed the greater improvement. Even among the small numbers involved, there was a significant difference between the non-toxic and toxic patients in the gold series as regards the mean number of joints affected at this point (non-toxic 5·5 and toxic 9·2 per patient).

If the initial level for each group is taken as 100 per cent. (right-hand section of Table V), then the number of joints affected in the non-toxic group at 12 months was reduced to 33 per cent. of the initial level, but in the toxic group to only 49 per cent. Subsequently, the number of joints affected increased in about the same proportion in both series.

Between the severe and less severe toxic groups, no significant differences could be demonstrated from these data.

In the control series, the non-toxic patients showed consistently greater improvement at every assessment than the toxic patients.

Strength of Grip (Table VI, overleaf)

The differences in the mean strength of either the right or the left grip at the start of the trial between the toxic and non-toxic groups were not statistically significant, but the strength of the left grip in the less severe toxic group in the gold series was significantly lower than that in the severe toxic group (Table VI).

Taking the mean of each group at Month 0 as 100, it is seen that the toxic group certainly did not improve more than the non-toxic group. Indeed, whilst the non-toxic group in the gold series improved the right grip by 25 per cent., and the left grip by 26 per cent. at 12 months, the toxic group improved by only 13 and 17 per cent. for the right and left grips respectively. Nor was there any real difference between the severe and less severe toxic patients in this respect. If anything, the patients with less severe toxicity fared better as regards the left grip.

As one would expect, no consistent pattern emerged in the control series.

Haemoglobin Concentration, Erythrocyte Sedimentation Rate, and Consumption of Analgesic Tablets

No Tables are presented for these indices, since the results were very similar to those already discussed.

Briefly, the toxic and non-toxic groups were similar at the outset as regards all these indices.

The haemoglobin levels of both the toxic and the non-toxic groups improved by 8 per cent. by Month 12, after which the mean concentration gradually fell again; only in the severe toxic group of the gold series was the level at Month 30 significantly below the peak figure at Month 12.

The erythrocyte sedimentation rate fell by Month 12 to 51 per cent. of the initial level in the non-toxic group, and to 56 per cent. in the toxic group; it then increased again but to a slightly greater extent in the toxic group.

The average number of analgesic tablets taken per patient per diem was the same for the non-toxic and toxic groups at every assessment.

TABLE V

MEAN NUMBER OF JOINTS AFFECTED (PER PATIENT) IN THE TOXIC AND NON-TOXIC GROUPS

Series	Month of Assessment	Mean Number of Joints Affected (per patient)				Trend			
		Non-Toxic	Toxic			Non-Toxic	Toxic		
			Total	Severe	Less Severe		Total	Severe	Less Severe
Gold	0	16·7	18·9	18·7	19·3	100	100	100	100
	12	5·5 S	9·2	8·8	9·9	33	49	47	51
	18	6·4	9·6	9·2	10·2	38	51	49	53
	30	7·6	10·6	11·3	9·3	46	56	60	48
	No. of Patients	46	31	20	11				
Controls	0	18·5	16·6	13·3	21·2	100	100	100	100
	12	11·2	15·2	15·1	15·2	61	92	114	72
	18	11·5	14·3	12·3	17·2	62	86	92	81
	30	10·3	13·0	8·6	19·2	56	78	65	91
	No. of Patients	70	12	7	5				

S = Significant difference between the toxic and non-toxic groups.

TABLE VI

MEAN STRENGTH OF GRIP (mm. Hg)
COMPARISON OF TOXIC AND NON-TOXIC GROUPS AT MONTHS 0, 12, 18, AND 30
(Mean Grip at Month 0 in Each Group = 100)

Series	Group		No. of Patients	Side	Month			
					0	12	18	30
Gold	Non-Toxic		46	R	143 ± 9 = 100	125	124	115
				L	143 ± 9 = 100	126	122	115
	Toxic	Total	31	R	156 ± 10 = 100	113	117	111
					159 ± 11 = 100	117	118	106
		Severe	20	R	159 ± 14 = 100	113	118	109
				L	174 ± 14 = 100	113	111	102
		Less Severe	11	R	152 ± 14 = 100	112	116	113
				L	S 131 ± 11 = 100	128	136	115
		Total	77	R	148 ± 7 = 100	120	122	114
				L	150 ± 7 = 100	121	120	111
Controls	Non-Toxic		70	R	147 ± 8 = 100	110	107	107
				L	148 ± 7 = 100	106	106	104
	Toxic	Total	12	R	141 ± 15 = 100	109	108	123
				L	127 ± 16 = 100	110	113	130
		Severe	7	R	133 ± 20 = 100	93	108	136
				L	121 ± 20 = 100	94	108	137
		Less Severe	5	R	152 ± 25 = 100	128	109	109
				L	136 ± 30 = 100	131	120	121
	Total		82	R	146 ± 7 = 100	110	108	109
				L	145 ± 7 = 100	107	107	108

R = Right hand. L = Left hand S = Significantly lower than left grip of "Toxic Severe" group.

Sheep Cell Agglutination Test

No comparison of the toxicity groups in the gold series by this index was possible, because only twenty of the 46 non-toxic patients and eighteen of the 31 toxic patients were tested at both Month 0 and Month 12.

Radiological Findings (Tables VII and VIII, opposite)

At the start of the trial the number of joints (per person) affected in any way varied only between an average of 6 and 7 per patient in the different groups. The mean number of joints which were narrowed was either two or three per patient—if we exclude the two very small control sub-groups (Table VII). Similarly, the mean number of erosions present varied only between 6 and 7 per person. No differences between the non-toxic and toxic groups or between the severe and less severe toxic groups existed therefore at the outset.

Radiological progression in the hands was measured by:

(*a*) The number of joints which narrowed, as a percentage of the number which *could* narrow (*i.e.* not initially narrowed);

(*b*) The mean number of new erosions—per assessable joint;

(*c*) The mean number of extensions of old erosions —per assessable joint.

Details of the methods of computation were given in the preceding Report. To reduce the tabulations it was considered sufficient to compare the toxicity groups by these three indices for the first period (0-18 months) and for the whole period (0-30 months) (Table VIII).

In the event (as the Tables show) there were no statistically significant differences between the toxicity groups as regards any of these indices either in the first period or over the whole duration of the trial. Nor was there even any suggestion that fewer joints narrowed or fewer new erosions developed in the toxic group. On the contrary, in the toxic group of the gold series, 7·8 per cent. of joints not initially narrowed became so in the first 18 months, compared with only 7·1 per cent. for the non-toxic group. Over the whole trial, 19 per cent. of the possible number narrowed in both the toxic and non-toxic groups. Similarly, the mean number of new erosions per assessable joint was higher (0·18) in the toxic than in the non-toxic group (0·16) during the first period; and over the whole trial the respective means were 0·32 and 0·23.

Contrasting the severe and less severe toxic sub-groups, the severe group showed, if anything,

TABLE VII

RADIOLOGICAL ASSESSMENT AT START OF TRIAL IN THE TOXIC AND NON-TOXIC GROUPS

Series	Group		No. of Patients	Mean per Person Both Hands Combined		
				Joints Initially Affected in Any Way	Narrowed Joints	Erosions Present
Gold	Non-Toxic		46	6·1	2·7	7·2
	Toxic	Total	29	6·7	2·9	6·9
		Severe	19	6·8	2·6	7·6
		Less Severe	10	6·5	3·4	5·5
Control	Non-Toxic		69	5·8	2·3	6·8
	Toxic	Total	12	6·8	2·7	6·7
		Severe	7	6·3	4·0	5·4
		Less Severe	5	7·4	0·8	8·4

TABLE VIII

RADIOLOGICAL PROGRESSION IN HANDS IN PATIENTS IN THE NON-TOXIC AND TOXIC GROUPS

Radiological Assessment	Group		Series			
			Gold		Control	
			0-18 mths	0-30 mths	0-18 mths	0-30 mths
(*a*) Joints which Narrowed (percentage of number which could narrow)	Non-Toxic		7·1 ± 1·8	19·3 ± 2·8	8·1 ± 1·2	19·1 ± 2·1
	Toxic	Total	7·8 ± 3·0	18·7 ± 3·7	8·2 ± 3·3	17·2 ± 5·6
		Severe	9·8 ± 4·5	20·0 ± 5·0	10·5 ± 4·5	19·6 ± 8·7
		Less severe	3·9 ± 1·8	16·3 ± 5·1	5·0 ± 5·0	13·8 ± 6·5
(*b*) Mean Number of New Erosions (per assessable joint)	Non-Toxic		0·16 ± 0·03	0·23 ± 0·04	0·20 ± 0·03	0·33 ± 0·04
	Toxic	Total	0·18 ± 0·04	0·32 ± 0·08	0·25 ± 0·06	0·42 ± 0·10
		Severe	0·19 ± 0·06	0·35 ± 0·11	0·27 ± 0·09	0·42 ± 0·17
		Less Severe	0·15 ± 0·05	0·26 ± 0·06	0·21 ± 0·10	0·41 ± 0·10
(*c*) Mean Number of Extensions of Old Erosions (per assessable joint)	Non-Toxic		0·09 ± 0·02	0·08 ± 0·02	0·08 ± 0·01	0·10 ± 0·02
	Toxic	Total	0·06 ± 0·02	0·10 ± 0·03	0·05 ± 0·02	0·07 ± 0·03
		Severe	0·07 ± 0·03	0·11 ± 0·04	0·04 ± 0·02	0·05 ± 0·03
		Less Severe	0·06 ± 0·03	0·09 ± 0·03	0·06 ± 0·03	0·10 ± 0·05

greater progression of the disease radiologically, but this degree was not greater than could be ascribed to chance.

Discussion

The two groups of patients, those who developed toxic reactions to gold therapy and those who did not, were in all main essentials comparable at the start of therapy. In the gold-treated series, 68 per cent. of the "toxic" group were initially in the two high grades (Functional Capacity Grades I and II) compared with 59 per cent. of "the non-toxic" group, and the toxic group appeared on the average slightly more "fit", on the patient's own assessment, than the non-toxic group. Nevertheless, not one of the indices used, including the radiological, indicated that those patients who developed toxic reactions fared any better at any stage of the trial than those who did not. Indeed, the evidence tended the other way: the numbers involved were small and most of the differences which emerged were no larger than could be ascribed to chance—but their consistency in favour of the non-toxic patients was a prominent feature throughout. The single statistically significant difference was the greater number of joints affected at Month 12 in the toxic group, a further point of advantage to the non-toxic group.

This trial does not, therefore, confirm the idea previously held by some clinicians that good therapeutic results are usually to be expected where gold salts have produced toxic effects. The evidence, indeed, slightly favours the opposite view.

Summary and Conclusions

(1) In the trial of gold therapy in rheumatoid arthritis reported in detail elsewhere in this *Journal* (Empire Rheumatism Council, 1961), 35 of a series of 99 patients treated with gold and 16 of a series of 100 controls developed toxic reactions, all but one during the course of injections. 77 of the gold series (31 toxic and 46 non-toxic) and 82 of the control series (12 toxic and 70 non-toxic) were followed for 30 months from the start of the trial.

(2) Comparing the clinical progress of those who developed toxic reactions with that of those who did not, no evidence was found that the toxic group fared better than the non-toxic by any of the indices used, including radiological examination. The only significant difference which emerged was that the number of joints involved at Month 12 in the gold-treated series was greater in the toxic than in the non-toxic group.

REFERENCE

Empire Rheumatism Council (1960). *Ann. rheum. Dis.*, **19**, 95.
—— (1961). *Ibid.*, **20**, 315.

Le rapport entre les réactions toxiques au cours de la chrysothérapie et l'amélioration dans l'arthrite rhumatismale

RÉSUMÉ ET CONCLUSIONS

(1) Au cours d'un essai de la chrysothérapie, rapporté ailleurs en détail (*Annals*, 1960, **19**, 95; 1961, **20**, 315), 35 malades appartenant à une série de 99 malades traités par des sels d'or et 16 malades d'entre 100 témoins manifestèrent des réactions toxiques. Toutes ces réactions, sauf une, survinrent pendant une série d'injections. Soixante-dix-sept de la série à l'or (31 "toxiques" et 46 "atoxiques") et 82 témoins (12 "toxiques" et 70 "atoxiques") furent surveillés pendant 30 mois dès le commencement de l'essai.

(2) En comparant les progrès des malades ayant accusé des réactions toxiques à ceux des autres on trouve que, selon tous les critères y compris un examen radiologique, les "toxiques" n'allaient pas mieux que les "atoxiques". La seule différence appréciable fut trouvée dans le nombre des articulations impliquées au bout de 12 mois dans la série des malades traités par des sels d'or; il y en eut plus chez les "toxiques" que chez les "atoxiques".

Relación entre las reacciones tóxicas durante la crisoterapia y las mejorías en la artritis reumatoide

SUMARIO Y CONCLUSIONES

(1) Durante una investigación de la crisoterapia, relatada detalladamente en otros artículos (*Annals*, 1960, **19**, 95; 1961, **20**, 315), 35 de una serie de 99 enfermos tratados con sales de oro y 16 de una serie de 100 testigos manifestaron reacciones tóxicas. Todas estas reacciones, menos una, ocurrieron durante una serie de inyecciones. Setenta-y-siete de la serie tratada con oro (31 "tóxicos" y 46 "atóxicos") y 82 de la serie de los testigos (12 "tóxicos" y 70 "atóxicos") fueron seguidos durante 30 meses desde el comienzo de la investigación.

(2) Al comparar el progreso de los enfermos que habían manifestado reacciones tóxicas con los demás se observa que, según todos los indicios incluyendo un examen radiológico, los "tóxicos" no se hallaron mejor que los "atóxicos". La sola diferencia significativa fué encontrada en la serie tratada con oro en el número de las articulaciones afectas al cabo de doce meses; este número fué mayor en los "tóxicos" que en los demás.

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STUDIES WITH RADIOACTIVE GOLD*

BY

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Although steroids, because of their more rapid action and ease of administration, have to some extent replaced gold compounds in the treatment of rheumatoid arthritis, there is evidence that, as regards both resistance to treatment and incidence of serious complications, gold compounds have the advantage (Kammerer and Cecil, 1958). The value of gold therapy has recently been confirmed by a double-blind trial (Empire Rheumatism Council, 1960). Minor complications are, however, frequent in patients treated with gold and may often necessitate interruptions in the course of treatment.

It would, therefore, appear advantageous to obtain more information on the pharmacology and mode of action of these compounds and particularly on the mechanism by which patients become either resistant or hypersensitive to them. Except that patients receiving small doses are more likely to be resistant and that the frequency of sensitivity reactions is independent of total dosage, little is known of the factors involved (Ellman, Lawrence, and Thorold, 1940).

Although chemical methods for the estimation of gold in blood and urine are available, these are technically difficult, and are of a degree of sensitivity which render the accurate assessment of the minute amounts occurring in the body fluids of patients under treatment with gold a matter of some uncertainty. Radioactive gold, on the other hand, can be estimated in amounts far below those found during therapy, and can, moreover, be detected in the tissues by scanning methods which enable the distribution throughout the body to be determined at frequent intervals after administration.

Distribution and Concentration in Body Fluids

The distribution of administered gold in the tissues has been studied both in experimental animals and in man. In guinea-pigs, De Witt (1918) studied the concentration of gold after the administration of four organic gold compounds. The highest concentration was found in the spleen with three of the four derivatives and in the lymph glands in the last. Lesser amounts were found in the liver, kidneys, and skin, and little elsewhere. In dogs, Eichelberger and McCluskey (1926) and Bertrand, Waine, and Tobias (1948) found that aurothiosulphate reached its greatest concentration in the kidneys with smaller amounts in the liver and spleen. Aurothioglucose was found by Swartz, Christian, and Andrews (1960) to concentrate most in the kidneys, but almost as much in the suprarenals after an interval of 30 minutes; lesser amounts were found in the spleen, liver, muscle and blood. Koppenhöfer (1936) found deposits chiefly in the liver, spleen, kidneys, and bone marrow. In healthy animals the gold was found chiefly in the parenchymal cells, in tuberculous animals in the reticulo-endothelial cells. Deposits have also been found in the suprarenal cortex and in the pituitary body. According to Michelazzi (1934), gold also enters the reticulo-endothelial cells of the synovial membrane. The quantity is small in healthy membrane, but much larger deposits are found in inflamed membrane with cellular proliferation. Bertrand and others (1948) similarly found a relatively high concentration in the synovial membrane, tendon, muscle, and bone in chemically-induced arthritis in rabbits. In a biopsy of synovial membrane from a patient with rheumatoid arthritis taken 24 hours after the injection of ^{198}gold sodium thiosulphate, they found much higher concentrations in the synovial membrane and fluid than in muscle, fascia, or skin. When sulphur is labelled in the thioglucose compound instead of gold, there is greater retention in all tissues except the liver, spleen, and kidneys, indicating that it is the gold itself which accumulates in the latter tissues (Swartz and others, 1960). The pharmacology of gold compounds has been studied in patients with rheumatoid arthritis by Freyberg, Block, and Levey (1941), Freyberg (1942), and Freyberg, Block, and Wells (1942), using a colorimetric method of assessment. In the blood, gold was found mainly in the plasma. Only insignificant traces were found in the cells. In the plasma, gold was found almost exclusively in the protein fraction. The plasma concentration of

* The cost of radioactive gold compounds for this investigation was covered by a grant from the Medical Research Council.

gold was found to vary in proportion to the weekly dose, remaining fairly constant when the weekly dosage was kept constant with no tendency to accumulate in the blood. Plasma concentrations following intramuscular injection were of the order of 0·5-1 mg./100 ml. for every 50 mg. gold administered in the weekly dose, whether this was in the form of aurothiomalate (Myocrisin), gold sodium thiosulphate, or aurothioglucose (Solganal B). If the drug was suspended in oil, the plasma concentration was rather lower (0·3-0·7 mg./100 ml.). Gold was excreted chiefly in the urine; faecal excretion was small and irregular though related roughly to the amount injected. In the urine, larger amounts were excreted on the day of injection, and tailed off rapidly thereafter, so that in a patient on weekly injections only some 15 per cent. of the administered dose actually appeared in the urine. Gold was found in the blood and urine after administration ceased, but in gradually decreasing amounts, for several months to a year. When a total of less than 500 mg. gold (1 g. Myocrisin) had been given, the excretion ceased earlier.

Calcium aurothiomalate in oil injected intramuscularly did not appear in the blood or urine at all during the first day, and even after this high values were seldom encountered. These, however, persisted much longer after administration ceased. In the skin, gold was found in concentrations of nil (in severe dermatitis) to 0·4 mg. per g. There was no relationship between gold content and skin reactions. Smith, Peak, Kron, Hermann, Del Toro, and Goldman (1958) compared the excretion of gold in four groups of rheumatoid patients: (1) responding to gold therapy, (2) relapsed during maintenance therapy, (3) with a low tolerance for gold, (4) showing little or no response. They found hyper-excretion in Groups 2 and 4 and hypo-excretion in Group 3.

Verhaeghe and Lebeurre (1954) used radioactive colloidal gold in human arthritis investigated by a scanning technique. Injected intramuscularly, gold appeared to pass selectively into one pathological joint, but another joint, apparently equally affected, showed little evidence of radioactivity. If injected into an arthritic knee joint, the gold could be detected over the liver, the bladder, and the other knee joint. Clemmeser (personal communication) found that gold combined chiefly with the alpha$_1$ globulin fraction in the plasma.

Material and Methods

The distribution of gold in the body was investigated in ten patients (Table I) by two techniques after the injection of radioactive gold:

(1) Zonal distribution throughout the body, using a scintillation counter;
(2) Concentration in blood, synovial fluid, and urine, using a wet counter.

In addition, biopsy specimens of skin, subcutaneous tissue, synovial membrane, and articular cartilage from a patient undergoing excision of an inflamed popliteal bursa were subjected after solution in aqua regia to gold assay in the wet counter.

Samples of blood (10 ml. from each patient) were collected in tubes containing Heller and Paul's potassium ammonium oxalate.

The gold was administered intramuscularly in the form of sodium aurothiomalate containing ^{198}Au.* The solution was supplied in two batches each containing 50 mg. sodium aurothiomalate in 5 ml., and having a total activity of 5 and 12 mc. respectively at the time of despatch. Approximately 1 ml. of this solution was

* Supplied by the Radiochemical Centre, Amersham, Bucks. Sodium aurothiomalate contains 50 per cent. gold.

TABLE I

PATIENTS STUDIED WITH RADIOACTIVE GOLD

Case No.	Criteria	Sex	Age (yrs)	Duration of Symptoms (yrs)	Number of Joints Affected	Sheep Cell Agglutination Test	Erythrocyte Sedimentation Rate at Time of Study (mm./hr)	Plasma Fibrinogen at Time of Study (mg. per cent.)
1	Responsive to Gold	M	71	2	7	1 : 128	32	670
2		M	61	15	4	1 : 64	10	330
3		M	52	7	13	1 : 4	7	350
4		M	45	7	8	1 : 128	5	330
5	Resistant to Gold	F	50	15	15	1 : 4	70	1,250
6		F	63	13	19	1 : 128	30	560
7		F	43	9	21	1 : 128	19	540
8	Hypersensitive to Gold	M	57	13	25	1 : 64	93	900
9		M	45	7	6	0	7	330
10	No Previous Gold	M	27	1	4	1 : 4	7	610

injected into each of ten patients suffering from rheumatoid arthritis, the site being the gluteal muscle in all except one, whose age made this site undesirable from the point of view of gonadal radiation. In eight of the patients the radioactive gold compound was injected alone. In Cases 2 and 3 it was mixed with the normal dose of natural gold. Seven patients were under treatment with gold at the time. All but one (Case 10) had had treatment with gold at some time previously. The patients were chosen to clarify various aspects of gold therapy, as shown in Table I. Of those described as resistant to gold, two (Cases 6 and 7) had made a satisfactory response initially, but had relapsed when the dosage was reduced or the treatment temporarily discontinued because of complications and had subsequently been resistant to further treatment. The third (Case 7) had shown no objective improvement throughout, despite continued high dosage. Of those hypersensitive to gold, one had a fixed skin eruption and was unable to receive even the smallest dose without suffering severe irritation with spread of the eruption. The other developed an eruption only when the disease became quiescent and could tolerate a sufficient dose to control the arthritis as soon as the disease became active again. Of the ten patients studied, six had a positive sheep cell agglutination test and seven had evidence, either from the erythrocyte sedimentation rate or from the plasma fibrinogen, of active disease at the time of the investigation.

Results

Blood Concentration of Gold.—The gold level in the plasma (Table II) varied from 0·11 to 0·17 mg./100 ml. (mean 0·15) on the first day after the injection. Thereafter it fell gradually, reaching a mean value of 0·02 mg./100 ml. by the end of the second week. The average value during the first week was 0·11, and for the second week 0·04 mg./100 ml.

The values in Cases 2 and 3, in which the radioactive gold was mixed with 25 mg. natural gold (Solganal B and Myocrisin respectively), do not differ substantially from the mean, indicating that the plasma level is directly proportional to the dose used. The lowest plasma levels were encountered in Cases 8 and 9, those who were hypersensitive to gold. In Case 9, a slightly lower dose of gold had been administered, but Case 8 had received the full amount. In Cases 5 and 6, who had received large amounts of gold in the past and who had become resistant, the plasma concentration fell more slowly and had reached about one-third of the initial value by the 16th day, whereas the mean had already fallen to one-seventh of the initial value by the 14th day. There was no obvious relationship between the plasma level and the activity of the disease.

Three samples of plasma taken on the 14th day were dialysed for 24 hours against tap-water. There was no reduction of the gold concentration, indicating that all the gold was combined with protein. In a sample of 5 ml. plasma, which was clotted by the addition of 0·03 ml. calcium chloride 40 per cent., the gold content of the serum was retested, and this was found to have one-third of the plasma concentration, indicating that much of the gold had attached itself to fibrin.

TABLE II

PLASMA CONCENTRATION OF GOLD AFTER INTRAMUSCULAR INJECTION

(mg./100 ml.)

Case No.	Dose of Sodium Aurothiomalate (mg.)	Day After Injection										
		1st	3rd	4th	5th	6th	9th	10th	11th	13th	14th	16th
1	10		0·10		0·10		0·05			0·03		
2	11	0·16	0·08			0·09			0·06		0·01	
3	11	0·17	0·09			0·09		0·06			0·009	
4	11	0·11		0·08		0·07			0·04		0·005	
5	11		0·12		0·11		0·07					0·05
6	12		0·11		0·14		0·08					0·04
7	11	0·15		0·13		0·11			0·06		0·01	
8	10		0·07		0·05		0·03					0·02
9	7		0·08		0·05		0·04					0·01
10	11	0·17		0·12		0·11			0·08			
Mean ..	10·4	0·15	0·13	0·11	0·09	0·09	0·05	0·06	0·06	0·03	0·02	

The red cell concentration of gold (Table III) was on an average about one-quarter of the plasma level on the first day after administration. Thereafter it fell, but less rapidly than the plasma level, so that by the end of the second week it approached and in some instances exceeded the latter.

TABLE III

RED BLOOD CELL CONCENTRATION OF GOLD
(mg./100 ml.)

Case No.	Day After Injection							
	1st	3rd	4th	6th	7th	10th	11th	14th
1					0·02			
2	0·03	0·01		0·02			0·01	0·006
3	0·03	0·02		0·03		0·02		0·01
4	0·02		0·01	0·01			0·01	0·01
7	0·06		0·02	0·03			0·01	0·01
9		0·02						
10	0·05		0·02	0·01			0·006	
Mean ..	0·04	0·02	0·02	0·02	0·02	0·02	0·01	0·008

Synovial Fluid.—Of the ten patients studied, seven had substantial effusions into one or both knee joints. Samples of synovial fluid were aspirated in the first instance on the 5th or 6th day after administering the gold, and again in five of the patients at the end of the 2nd week (Table IV). The gold levels in the synovial fluid were all slightly lower than those in the plasma on the 5th and 6th day, the mean value in the synovial fluid being 0·07 mg./100 ml. as against 0·09 mg. in the plasma. At the end of the second week, the mean values in synovial fluid and plasma were identical (0·02 mg./100 ml.), but in one sample the synovial fluid level was then four times the plasma level.

TABLE IV

SYNOVIAL FLUID CONCENTRATION OF GOLD
(mg./100 ml.)

Case No.	Day After Injection			
	5th	6th	14th	15th
2		0·06	0·003	
4		0·05	0·02	
5	0·08			0·04
6	0·07			0·02
7		0·10		
8	0·04			0·01
10		0·10		
Mean ..	0·07		0·02	

Tissue Concentrations.—In Case 7, a popliteal bursa had for some time been causing much discomfort. It was therefore decided to excise it, and this was done by Mr. F. R. Zadik on the 15th day after the administration of radioactive gold. The bursa, which weighed 30 g. and contained 15 ml. fluid with fibrin clot, was found to communicate with the knee joint, the aperture being obstructed by a plug of fibrin. Samples were taken of articular cartilage, skin, and subcutaneous fat. Each tissue was dissolved in 10 ml. aqua regia, and the concentration of radioactive gold was estimated. The fibrin clot from the bursa was similarly treated. The concentrations of gold were as follows:

Tissue	Concentration of Radioactive Gold (mg./100 g.)
Skin	0·05
Subcutaneous Fat	0·12
Synovial Membrane	0·02
Cartilage	0·64
Fibrin Clot (from Bursa)	0·67

There was thus a very high concentration in both the fibrin clot and the articular cartilage. The latter must be accepted with caution as only a very small sample (0·03 g.) was available.

Urinary Excretion of Gold.—As the patients taking part in this study were all out-patients, the collection of 24-hr specimens of urine was of necessity somewhat patchy and complete information is thus not available (Table V, opposite). As in Freyberg's series, maximal excretion occurred on the first day, when some 5 per cent. of the administered gold was excreted. By the end of the first week an average of 1·68 mg. (*i.e.* some 15 per cent. of the dose) had been passed in the urine, and by the end of the second week 1·94 mg. (*i.e.* some 20 per cent. of the dose) had appeared. Excretion by this time was slight and further measurements were impossible. There was no obvious relationship between excretion and disease activity. Cases 5 and 6, who were resistant to gold, did not excrete it more rapidly; indeed, their excretion was on most days below the average.

Zonal Distribution of Gold.—Five patients (Cases 1, 5, 6, 8, 9) were investigated with the aid of the scintillation counter.

TABLE V

DAILY EXCRETION OF GOLD IN URINE

(mg./24 hrs)

Case No.	Day After Injection														
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th
1		0·15	0·21	0·14	0·16	0·10	0·10	0·15	0·11	0·12	0·12	0·14	0·003	0·008	0·005
2	←——1·35——→			0·23	0·20	0·13	0·11			0·07					
3		0·11	0·11		0·10		0·07			0·008					
4	0·82	0·13	0·14	0·23	0·24	0·13	0·11	0·09		0·01	0·03	0·01			
5			0·12	0·06	0·05	0·05	0·02	0·002	0·002	0·002					
6		0·17	0·08	0·11	0·07	0·1	0·09	0·07	0·01						
7	0·33	0·16	0·14	0·104	0·16	0·12	0·3								
8		0·3		0·10	0·10	0·10		0·01		0·01					
9			0·17	0·18	0·16	0·10	0·12	0·08	0·12		0·006	0·002	0·006		
10	0·24	0·36	0·1	0·1	←——0·45——→										
Average ..	0·46	0·20	0·13	0·13	0·14	0·10	0·12	0·07	0·05	0·03	0·05	0·05	0·005	0·008	0·005

Absorption of gold began almost immediately after injection and within 5 minutes it could be detected in all parts of the trunk and in the proximal parts of the limbs. Within 15 minutes counts were obtainable over the hands and feet.

The highest counts were made during the first 2 weeks over the site of injection and the lowest over the fingers and feet, with intermediate values over the remainder of the trunk, diminishing towards the periphery. The values were in general proportional to the mass of tissue in the vicinity of the counter. Radioactivity continued to be distributed in this way up to the 20th day, when the site of injection ceased to give the highest values, which were then encountered over the liver, spleen, or kidneys. After the 21st day, owing to reduction of radioactivity, the values even at these sites came so close to the background level that the results were extremely variable and ceased to be reproducible.

As an illustrative example, average values of all readings taken between the 2nd and 16th days after injection are shown for Patients 1, 5, and 6 in Figs 1, 2, and 3 (overleaf), together with the mean concentrations in the plasma and where available the synovial fluid concentration of gold. All the counts were corrected after deduction of the background count for deterioration of radioactivity to the theoretical count on the day of administration of the gold. The higher of the two gluteal counts indicates the side which was injected and this is associated with a higher count in the iliac fossa on the same side. Counts in the loins and midthighs and at other sites, on the other hand, show no relationship to the side injected.

In all patients so examined, higher counts were obtained over the right than over the left hypochondrium and the former in general gave, apart from the injection site, the highest count of any part of the body. The pectoral regions and loins gave, on the whole, somewhat similar values to those of the left hypochondrium and to the iliac fossa on the opposite side of the body from the injection site. In scanning the limbs, the hips were excluded because of their proximity to the site of the injection. All joints of the fingers were grouped together and also all joints of the feet. Thus, in each patient, fourteen joints or groups of joints were scanned. Of the seventy "joints" scanned in this group of five patients, forty were in sequence with the non-articular zones, six gave values which were too low, and 24 gave values which were too high to be in sequence. 35 of the seventy joints scanned were giving rise to symptoms at the time of examination; of these, seventeen gave too high a count compared with seven of the 35 painless joints. This difference is significant ($P = 0{\cdot}04$). The high counts found over painful joints were not limited to the early stages of the investigation when the gold was mainly in the blood stream, but persisted throughout the 19 days of the study.

The two patients resistant to gold who were

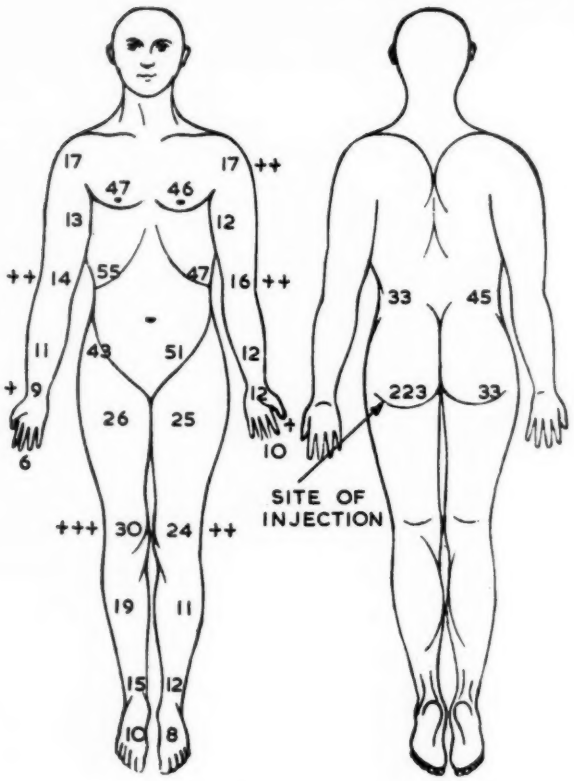

Fig. 1.—*Patient* 1, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1 mc. in 10 mg. sodium aurothiomalate.
Average plasma gold: 0·07 mg./100 ml.

In this and subsequent figures, the plus signs indicate presence and severity of pain and tenderness.

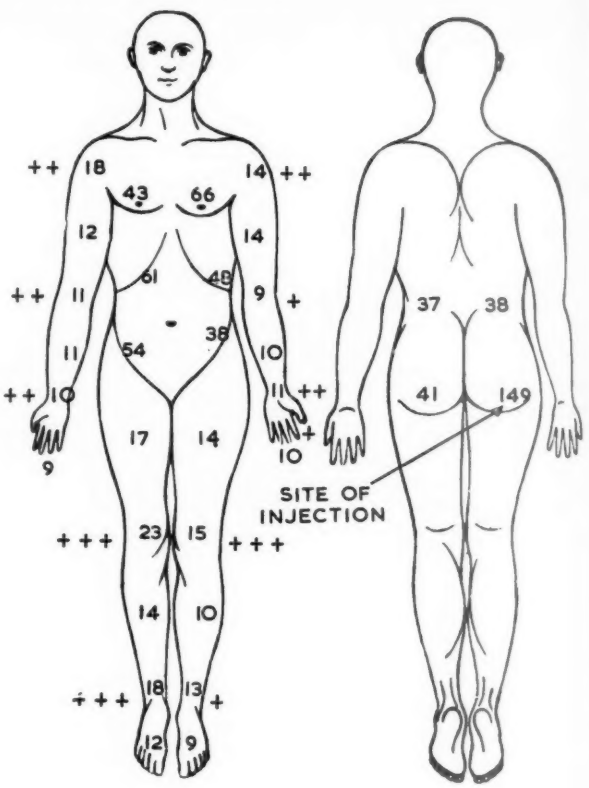

Fig. 2.—*Patient* 5, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1 mc. in 10 mg. sodium aurothiomalate.
Average plasma gold: 0·08 mg./100 ml.
Average synovial fluid gold: 0·06 mg./100 ml.

Fig. 3.—*Patient* 6, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·09 mg./100 ml.
Average synovial fluid gold: 0·05 mg./100 ml.

Fig. 4.—*Patient* 6, average counts per second during the first and second day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Plasma gold: 0·11 mg./100 ml.

Fig. 5.—*Patient* 6, average counts per second during 3rd to 7th day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·14 mg./100 ml.
Average synovial fluid gold: 0·07 mg./100 ml.

Fig. 6.—*Patient* 6, average counts per second during the 8th to 16th day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·06 mg./100 ml.
Average synovial fluid gold: 0·02 mg./100 ml.

examined with the scintillation counter (Cases 5 and 6, Figs 2 and 3) showed no evidence of hold-up at the site of injection, and had an adequate concentration in the plasma and synovial fluid and in the region of the affected joints.

The progress of events during the first 16 days after administration is illustrated in Patient 6 (Figs 4 to 6). There was a progressive fall in the count over the site of injection. Over the trunk in general, the count did not change though there was a slight rise over the liver and spleen. Over the limbs on the other hand, the count tended to rise progressively. This increase did not occur more in the joints than over the inter-articular zones and was not particularly related to the sites of pain. It was, however, somewhat patchy in distribution. These changes occurred despite a falling plasma and synovial fluid level and continued excretion of gold in the urine.

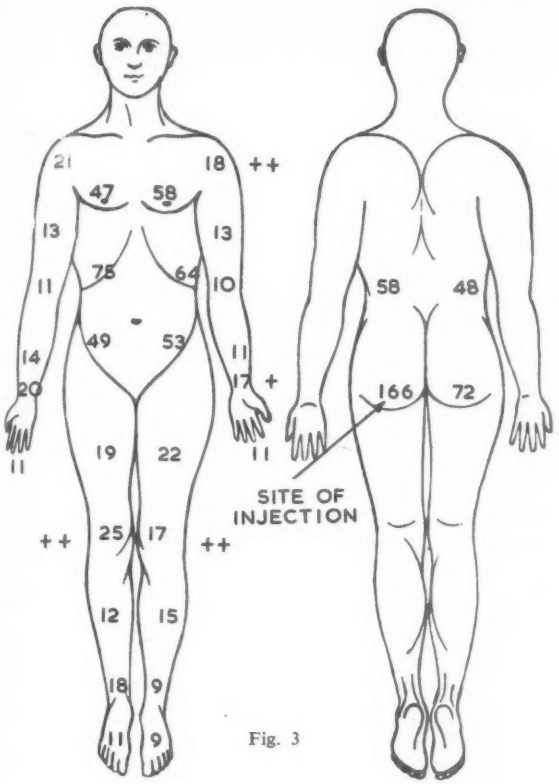

Fig. 3

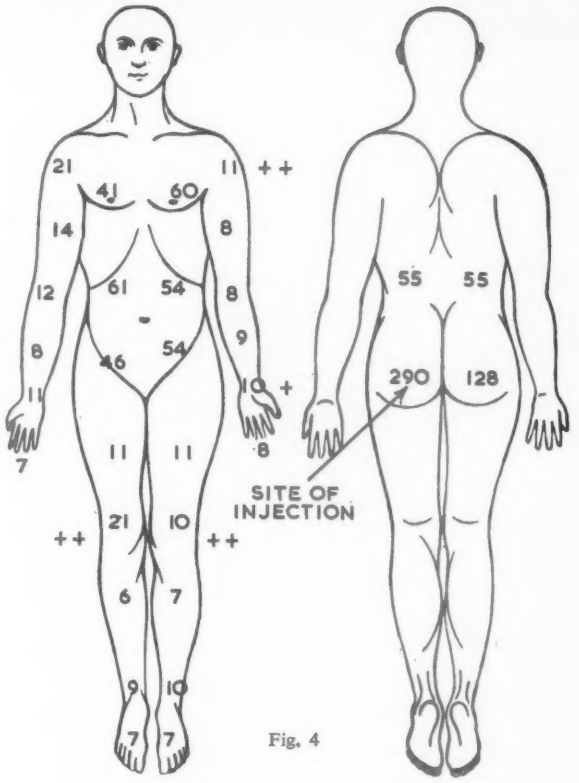

Fig. 4

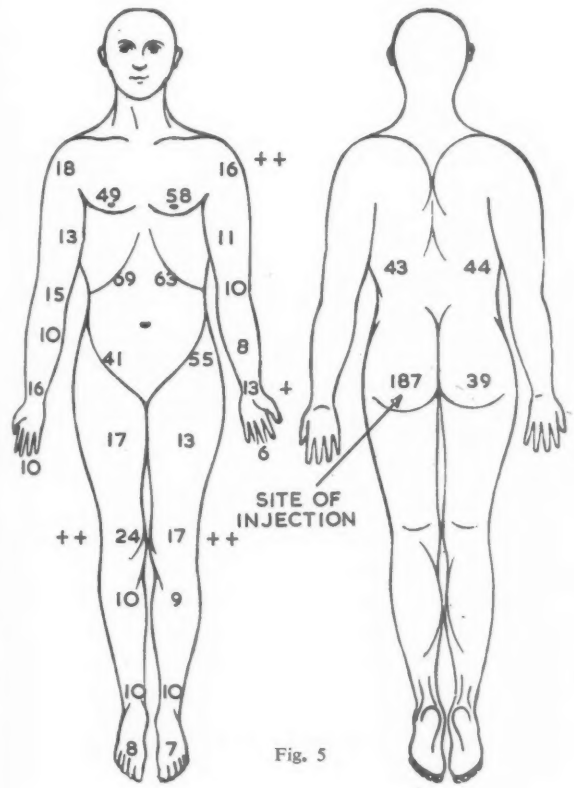

Fig. 5

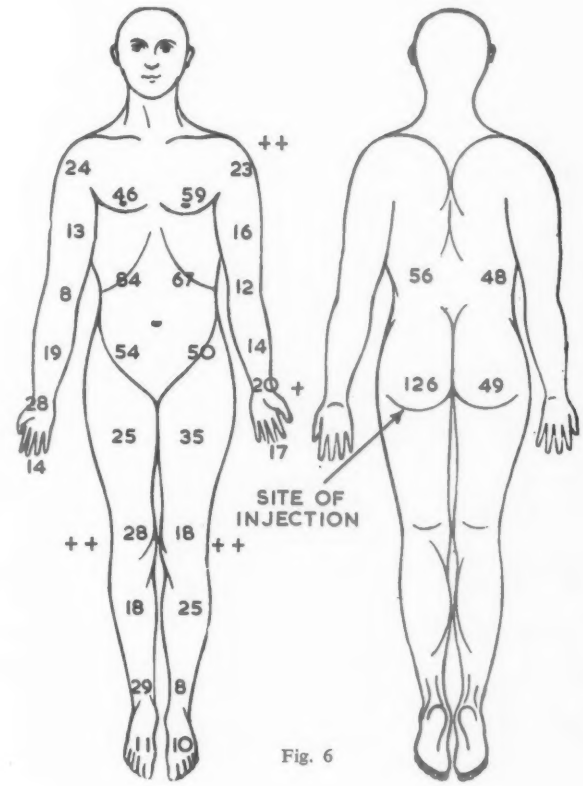

Fig. 6

Changes in counts in the remaining four patients were similar. In some, however, there was a progressive increase in counts in both trunk and limbs. In one (Case 1), the corrected count at the site of injection also showed a progressive increase, reaching a maximum on the 11th day and thereafter subsiding. This may have been due to diffusion towards the skin, possibly from lymphatic spread.

In those joints over which the counts were relatively high and out of sequence, it may be said that the difference was greater at first when the blood level was high and became less in the later stages as the blood and synovial fluid levels fell.

Discussion

The plasma levels assessed by using radioactive gold are higher than those of Freyberg and others (1941, 1942) using a colorimetric method. In general it may be said that their plasma level is in the region of 0·5 to 1 mg./100 ml. for every 50 mg. administered. In Cases 2 and 3, in which a combined dose of radioactive and inactive gold totalling 30 mg. each had been given, the total gold level may be calculated from the figures for radioactive gold as 0·5 to 1·0 mg./100 ml. in the first week.

The high proportion of gold which is combined with protein in the plasma is confirmed by the dialysis experiments carried out in this study. According to Libenson (1945), the gold-protein complex *in vitro* does not release gold ions in solution, but in view of the presence of gold in the urine, and as this was found in the absence of proteinuria, it is evident that some uncombined gold is present *in vivo*. According to Simon (1954), gold in plasma is combined with the β and α_2 fractions. It would appear, however, from the plasma-serum difference encountered in this study, that a proportion of the gold is combined with fibrinogen.

The distribution of gold in the body as measured by scanning confirms the experimental findings. However, the interpretation of tissue concentrations, whether determined by scanning or by direct estimation on tissue samples, must be accepted with caution. As the gold is probably at first confined to the blood stream by reason of its protein binding, tissue levels of gold will at first be a measure of vascularity and thus, indirectly, of the presence of inflamed tissue. Only when the blood level has become very low will a true measure of tissue concentration be obtained. This may explain the difference between the low concentration in synovial membrane in my own patient on the 15th day and the high values encountered by Bertrand and others (1948) on the first and fifth day after injection. The fact that high scanning counts over certain joints persisted into the third week may depend on the deposition of gold in other joint tissues (*e.g.*, the articular cartilage) or on the presence of gold combined with the fibrin deposits which abound in rheumatoid joints. The relatively high value in subcutaneous fat in Case 7 suggests that gold may to some extent combine with the fat. It was not found in the fatty layer, which separated from the extracting fluid, but this would not be expected, since any gold compound would be broken down in the presence of aqua regia.

Previous workers do not seem to have made any estimate of gold concentrations in articular cartilage, whether normal or diseased, and the values obtained on a single small sample cannot be taken as indicative of those encountered in diseased cartilage as a whole. Dunstone (1959) found that, whereas normal cartilage shows equal binding capacities for sodium, potassium, magnesium, calcium, strontium, and barium ions and these correlate equally with the sulphate content, copper and beryllium were bound to a greater extent. This he attributed to the greater binding by chondroitin sulphate of multinuclear ions. It is possible that a similar affinity exists for gold.

If, however, a concentration of the order of 0·6 mg./100 g. is commonly encountered after a dose of 10 mg. of a gold compound, and if with higher dosage there is a proportionate increase, doses up to 200 mg. should result in values of the order of 12 mg./100 g., possibly with further increases on repeated administration. Since a therapeutic effect is seldom apparent before the fifth injection, it would seem likely that the concentration resulting from a single dose is inadequate. In searching for a possible mode of action of gold, we must, therefore, consider pharmacological effects occurring with concentrations possibly of the order of 20 mg./100 g.

No satisfactory explanation of the mechanism by which gold produces its effect has been forthcoming. Chrysotherapy was first introduced by Forestier (1929) on the assumption that tuberculosis has an aetiological relationship to the disease, but of this there has been no satisfactory proof. Other workers have suggested an effect on tissue uptake of oxygen or on glutathione metabolism. Clinical experience with gold treatment would suggest that gold may have a general anti-inflammatory effect,

since it has a pronounced effect, when given in high dosage, on both the erythrocyte sedimentation rate and the degree of joint swelling (Ellman and Lawrence, 1938). Moreover, it is common experience that ulcers on the gums due to badly fitting dentures do not heal so rapidly in patients receiving gold. Skin infections such as boils also tend to be refractory. Perforation or haemorrhage from peptic ulceration of the stomach or duodenum also appear more frequently, in the author's experience, in persons receiving high dosages of gold.

It is known that heavy metals are powerful enzyme inhibitors and that this inhibition tends to be specific and may occur at a high dilution, apparently by blocking those groups in the enzyme which are responsible for its specificity. In the living cell the effect is enhanced by the fact that, even though the metal is in low dilution in the surrounding medium, a considerable quantity may be fixed by the cell (Dreschel, 1921). Enzymes are thought to play a part in the process of inflammation at several stages and it seems likely that enzyme responses are similar to those encountered in non-rheumatoid subjects.

According to Ungar (1952), when a cell is damaged, an enzyme cytofibrokinase is released. This in turn releases the proteolytic enzyme fibrinolysin from a precursor profibrinolysin, which is present in plasma in association with the euglobulin fraction and is thought also to exist in the tissues. Fibrinolysin, like trypsin, is capable of breaking down a wide variety of protein substances. According to Ungar, by breaking down cell protein, it releases histamine, heparin, and certain polypeptides. The polypeptides have the property, not only of producing pain, but also of increasing capillary permeability, and would thus be capable of causing the changes found in inflammation.

A natural proteolytic inhibitor is found in normal serum (Landsteiner, 1900) and several drugs have been shown also to act as anti-fibrinolysins. These include salicylic acid, antipyrine, amino-pyrine, 3-hydroxy 2-phenylcinchoninic acid, and p-aminophenol. The administration of cortisone or ACTH also results in an increased anti-fibrinolytic activity of the serum (Ungar, 1953).

The natural proteolytic inhibitor is increased in diseases associated with increased tissue destruction, and in general parallels the erythrocyte sedimentation rate and the fibrinogen plasma level (Shulman, 1952). In rheumatoid arthritis, for example, serum anti-fibrinolytic activity is related to the activity of the disease process. Fibrinolysin on the other hand, is reduced in rheumatoid arthritis, particularly in the less active forms, rising to a normal level when the disease becomes very active (Thomas and Dingle, 1955).

With a view to elucidating the possible inhibitory effects of gold on inflammatory enzymes, a number of experiments have been made by the author. Although these have appeared to indicate an inhibitory effect on clot lysis by streptokinase from aurothioglucose in concentrations as low as 2 mg./100 ml. in some experiments, the effect has not been consistent and aurothiomalate has not been found to have a similar action. This could be interpreted as indicating that aurothiomalate is converted into another compound in the body, but it is not proposed to lay claim to the correctness of these views till further work has been done.

The information on the causes of gold resistance and gold hypersensitivity which has been derived from this study is mainly of a negative character. Indeed, the absence of any relationship between excretion of and tolerance to gold would appear at first sight to contradict the findings, already referred to, of Smith and others (1958). In their two patients with toxic reactions, excretion of gold was diminished, whereas in the present study it was, if anything, increased. In their study, however, excretion was measured just before the onset of dermatitis, whereas in the present cases skin reactions had been present for several months or years. A possible explanation is that a rapid passage of gold into the tissues is associated with the onset of sensitivity and that this results in a transient decrease of the excretion in the urine. With regard to gold resistance, Smith and others (1958) found that 17 to 28 per cent. of the administered dose was excreted in one week after the injection of gold in resistant patients receiving 12 to 50 mg. weekly compared with an average excretion of 14 per cent. of the dose in responding patients. In the present study, only 13 per cent. of the administered dose was excreted by resistant patients, the same amount being the average for the whole series. When the dose was increased to 100 mg. weekly, the patients in Smith's series went into remission, but in the present study the resistant patients received 200 mg. weekly for prolonged periods without benefit. It is thus apparent that, though drug resistance may, in patients receiving relatively small doses, be due to high excretion, other factors (possibly the presence of extensive fibrin deposits capable of binding the gold ions and rendering them biochemically inactive) may be responsible for the more extreme examples of drug resistance.

Summary

The distribution of gold in the body was investigated in ten patients with rheumatoid arthritis. These included four who were responsive to gold, three who were resistant, two who had developed hypersensitivity reactions, and one who had not previously received gold. Aurothiomalate, containing ^{198}Au, was injected intramuscularly as a single dose of 10 mg., and its subsequent distribution was followed by means of a scintillation counter. The concentration in blood, synovial fluid, and urine was also determined.

The plasma level varied from 0·11 to 0·17 mg./100 ml. on the first day and thereafter fell gradually to a mean value of 0·02 mg./100 ml. by the end of the second week. Where radioactive gold was mixed with inactive gold, the plasma levels of the radioactive variety were in the same range, indicating that the blood level was directly proportional to the dosage used.

The lowest plasma levels were encountered in two patients who were hypersensitive to gold. The slowest fall in the plasma level occurred in two patients who had become resistant to gold therapy. There was no relationship between the plasma level and the activity of the disease process.

The gold in the plasma appeared to be completely bound to protein mostly to fibrinogen. The red cell concentration of gold varied from one-quarter of the plasma level on the first day to a value equal to or greater than the plasma level by the end of the second week. The concentration in the synovial fluid was slightly less than that in the plasma at the end of the first week, but became equal to or greater than the plasma level by the end of the second week. Fluid and fibrin clot from a popliteal bursa removed at operation showed a gold concentration of 0·67 mg./100 ml. (plasma level 0·01 mg./100 ml.). A similar high concentration was found in a biopsy sample of articular cartilage from the same patient.

The injected gold was excreted slowly in the urine, 15 per cent. in the first week, and 20 per cent. by the end of the second week, by which time very small quantities were being passed. Excretion was unrelated to disease activity or response to therapy, but was more rapid in patients with sensitivity reactions.

Apart from the site of injection, the highest scanning counts were obtained over the right hypochondrium, but high values were also noted over the left hypochondrium, pectoral regions, and loins. In the limbs, the counts were greatest proximally and diminished as the scanner was moved peripherally. Of the seventy joints scanned, forty gave counts in sequence with the non-articular zones, six gave counts which were lower and 24 counts which were higher than those expected from their position in the limb. Painful joints gave high counts 2·5 times more often than symptomless joints. This phenomenon was not limited to the period of time immediately following the injection but persisted when the level in the blood had become negligible.

It is suggested that gold compounds may have a local action on inflamed tissues by inhibition of the enzymes concerned in the inflammatory process.

I wish to express my gratitude to Dr. R. Harris for the loan of the scintillator equipment and for his advice on its use, to Drs B. Slack and W. Emery for advice on wet counting methods, and to Dr. J. Ball for estimating the results of the sheep cell agglutination tests.

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Études avec l'or radioactif

RÉSUMÉ

La distribution d'or dans l'organisme fut étudiée chez dix malades atteints d'arthrite rhumatismale. Sur ces dix cas, quatre étaient réceptifs à l'or, trois y étaient résistants, deux avaient manifesté des réactions d'hypersensibilité et un recevait de l'or pour la première fois. On injectait par voie intramusculaire une seule dose de 10 mg. d'aurothiomalate contenant la forme radioactive ^{198}Au et on déterminait sa distribution dans l'organisme au moyen d'un scintilloscope. Le taux d'or dans le sang, le liquide synovial et l'urine était aussi déterminé.

Le taux sanguin oscillait entre 0,11 et 0,17 mg. par 100 c.c. le premier jour, baissant progressivement pour atteindre une moyenne de 0,02 mg. par 100 c.c. à la fin de la deuxième semaine. Quand on mélangeait l'or radioactif avec de l'or inactif, les taux sanguins de la forme radioactive étaient au même niveau, indiquant que le taux sanguin était directement proportionnel au dosage employé.

Les taux sanguins les plus bas furent trouvés chez les deux malades hypersensibles à l'or. La baisse la plus lente du taux sanguin se produisit chez deux malades devenus résistants à l'aurothérapie. Il n'y eut pas de rapport entre le taux sanguin et l'activité de la maladie.

L'or sanguin semblait être complètement lié à la protéine, surtout au fibrinogène. Le premier jour, le taux d'or érythrocytaire était quatre fois moindre que le taux plasmatique, mais vers la fin de la deuxième semaine il lui devenait égal et même supérieur. Dans le liquide synovial il y avait un petit peu moins d'or que dans le plasma pendant la première semaine, mais il y en avait autant ou plus vers la fin de la deuxième semaine. Le liquide et un caillot fibrineux d'une bourse poplitée enlevée à l'opération ont montré un taux d'or de 0,67 mg./100 c.c. (taux plasmatique 0,01 mg./100 c.c.). Des taux aussi élevés ont été trouvés dans un échantillon biopsique d'un cartilage articulaire du même malade.

L'or injecté était excrété lentement dans l'urine: 15% pendant la première semaine et 20% au bout de la seconde, après quoi l'élimination se faisait en très petites quantités. L'excrétion procédait indépendamment de l'activité morbide ou de la réponse thérapeutique, mais elle était plus rapide chez des malades accusant des réactions de sensibilité.

En dehors de l'endroit de l'injection, le scintilloscope donnait les plus grands chiffres à l'hypocondre droit, mais le chiffre était aussi élevé à l'hypocondre gauche, dans la région pectorale et lombaire. Dans les membres, le maximum des scintillations était dans la partie proximale, diminuant à mesure qu'on passait l'appareil vers l'extrémité. Sur 70 articulations examinées au scintilloscope, 40 ont donné des chiffres en concordance avec les zones non-articulaires, dans 6 ces chiffres ont été inférieurs et dans 24 supérieurs à ceux calculés pour la position respective dans le membre. Les articulations douloureuses donnaient des chiffres élevés 2,5 fois plus souvent que les articulations asymptomatiques. Ce phénomène n'était pas limité à la période immédiatement après l'injection, mais persistait quand le taux sanguin devenait negligeable.

On suggère que les sels d'or peuvent exercer une action locale sur des tissus inflammés par l'inhibition des enzymes impliqués dans le processus inflammatoire.

Estudios con el oro radioactivo

SUMARIO

La distribución de oro en el cuerpo fué estudiada en diez enfermos con artritis reumatoide. Entre ellos hubo cuatro casos con buena respuesta terapéutica al oro, tres casos resistantes, dos con manifestaciones de hipersensibilidad y uno que no había recibio auroterapia anterior. Se inyectaba por vía intramuscular una sola dosis de 10 mg. de aurotiomalato conteniendo la forma radioactiva ^{198}Au y se estudiaba su distribución en el cuerpo por medio de un "centellometro" (*scintillation counter*). Se determinó también la concentración de oro en la sangre, el líquido sinovial y la orina.

Las cifras plasmáticas variaban entre 0,11 y 0,17 mg. por 100 c.c. durante el primer día, bajando poco a poco y alcanzando una media de 0,02 por 100 c.c. al cabo de la segunda semana. Cuando se mezclaba el oro radioactivo con el inactivo, las cifras de la forma radioactiva quedaban al mismo nivel, indicando así que la concentración sanguínea es directamente proporcional a la dosis empleada.

Las más bajas concentraciones sanguíneas fueron encontradas en los dos enfermos hipersensibles al oro. La más despacia baja de la concentración sanguínea ocurrió en dos enfermos que adquirieron resistencia a la auroterapia. No hubo relación entre la tasa plasmática y la actividad de la enfermedad.

El oro sanguíneo parecía estar completamente ligado a proteinas, particularmente al fibrinógeno. El primer día la cifra del oro eritrocitario fué cuatro veces menor que la del oro plasmático, pero hacia el fin de la segunda semana fué igual o mayor. En el líquido sinovial hubo algo menos de oro que en el plasma durante la primera semana, pero al cabo de la segunda semana el oro sinovial alcanzaba o rebasaba la tasa plasmática. El líquido y un coágulo fibrinoso de una bolsa poplitea extirpada en una operación dieron una concentración de oro de 0,67 mg. por 100 c.c. (en el plasma 0,01 mg. por 100 c.c.). Similares concentraciones altas fueron encontradas en un espécimen de biopsia del cartílago articular del mismo enfermo.

El oro inyectado fué eliminado lentamente en la orina: el 15% durante la primera semana, el 20% durante la segunda y luego muy pequeñas cantidades fueron excretadas. La excreción fué independiente de la actividad mórbida o de la respuesta terapéutica pero fué más rápida en enfermos con reacciones de sensibilidad.

Fuera del sitio de la inyección, el centellómetro dió los mayores resultados en el hipocondrio derecho, pero altas cifras fueron también obtenidas en el hipocondrio izquierdo, las regiones pectorales y lumbares. En los miembros, las cifras fueron mayores proximalmente. disminuyendo al pasar el aparato hacia la extremidad, Sobre 70 articulaciones examinadas, 40 dieron cifras en conformidad con las zonas no-articulares, en 6 estas cifras fueron inferiores y en 24 superiores a las anticipadas según la posición en el miembro. Articulaciones

doloridas dieron cifras altas 2,5 veces más frecuentemente que articulaciones asintomáticas. Este fenómeno no se limitaba al período inmediatamente después de la inyección, sino persistía cuando la concentración sanguínea era mínima.

Se sugiere que los compuestos de oro pueden ejercer una acción local sobre tejidos inflamados por inhibición de enzimas implicadas en el proceso inflamatorio.

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JOINT SYMPTOMS IN MYELOMATOSIS AND SIMILAR CONDITIONS*

BY

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The commonest presenting symptom in myelomatosis is pain in the back, which is frequently associated with vertebral collapse. Subsequently the patient may complain of sciatica or brachial neuralgia due to nerve root pressure. This may be a direct result of the collapse, or in some cases may be caused by an extradural plaque of myeloma cells. A less common but well-recognized presentation is a polyarthritis, which superficially resembles rheumatoid arthritis and is usually treated as such in the first instance. 24 cases of this type have now been reported in the literature; among the most important reports are those of Magnus-Levy (1938), Stewart and Weber (1938), Tarr and Ferris (1939), and Davis, Weber, and Bartfeld (1957). Such a patient is middle-aged and develops an arthritis which may or may not be painful. The pattern of joint involvement is variable, but the small joints of the hands frequently become swollen. A careful examination may reveal the presence of nodules in the neighbourhood of joints, attached to bony prominences, or in skeletal muscle, and in two of the thirteen cases reviewed by Tarr and Ferris there was macroglossia. Biopsy or autopsy examination of affected joints or of nodules will show infiltration with para-amyloid. This apparent arthritis frequently precedes any overt manifestations of myelomatosis, but it can develop during the course of the disease. It should not be confused with pain seeming to arise in joints from myelomatous involvement of adjacent bone, which is not uncommon in the hips and shoulders.

Recently we have seen several patients with arthritis who on subsequent investigation have been found to have myelomatosis, and the purpose of this paper is to review these cases against a background of all cases of myelomatosis seen at the Hammersmith Hospital, and at the Canadian Red Cross Memorial Hospital, Taplow, during the past 10 years. Six other relevant cases are also reported: two of rheumatoid arthritis and macroglobulinaemia, two with a myeloma-like protein in the peripheral blood but no other manifestations of myelomatosis, and two with primary amyloidosis.

The 46 cases of myelomatosis included in this survey were seen during the 10-year period from January, 1950, to January, 1960; in all cases the diagnosis had been unequivocally confirmed by sternal marrow examination, tumour biopsy, or at autopsy. The clinical features present in the 46 cases are summarized in Table I.

TABLE I

CLINICAL AND LABORATORY DATA IN 46 CASES OF MYELOMATOSIS

Total Number of Cases		46	Percentage
Male : Female Ratio		26 : 20	
Average Age at Onset (yrs) (range 35–75)		57	
No. Alive at End of Study		22	48
Mean Duration to Last Follow-up (yrs) (range 6 wks to 9 yrs)		2·4	
No. Died (*Post mortem* Examination Taplow 4, Hammersmith 15)		24	52
Mean Duration of Life (yrs) (range 2/12–7)		2·2	
Bone Pain		42/46	91
Raised Erythrocyte Sedimentation Rate (mm./hr, Westergren)	0–50	4/30	13
	51–100	10/30	33
	101 or More	16/30	54
Myeloma Peak on Electrophoresis		25/34	73
Bence Jones Proteose		18/44	41
Proteinuria		22/44	50
Osteolytic Lesions on *X* Ray		39/45	87
Hypercalcaemia 12 mg. per cent. or More		10/25	40
Alkaline Phosphatase 15 K.A. Units or More		3/25	12

* Read at a meeting of the Heberden Society on December 1, 1961.

Of these patients 24 have died and the autopsies performed in nineteen of them confirmed the diagnosis. The mean duration to death was 2·2 years (range 2 months to 7 years), and this compares with a mean duration to last follow-up in the other 22 cases of 2·4 years (range 6 weeks to 9 years). One of the most prominent symptoms was bone pain, and this was present at some stage of the disease in 42 (91 per cent.) of the cases.

Laboratory investigations revealed erythrocyte sedimentation rates of 101 mm. or over in 1 hour in 54 per cent. of thirty cases examined, and in 33 per cent. the rate lay between 51 and 100 mm. Examination of the plasma proteins showed a reversed albumin/globulin ratio in 70 per cent. In 34 cases in which electrophoresis was performed, 73 per cent. showed a distinct myeloma peak in the beta- or gamma-globulin region. Bence Jones proteose was detected in the urine in 41 per cent. of cases at some stage in the disease.

Radiological examination showed the presence of definite osteolytic lesions in 87 per cent. Hypercalcaemia of 12 mg./100 ml. or more was present in 40 per cent. of 25 cases, but in only 12 per cent. of these was the alkaline phosphatase raised above 15 King-Armstrong units.

The musculo-skeletal manifestations seen in these 46 cases are shown in Table II. Bone pain was usually felt in the lumbar or dorsal spine, often associated with vertebral collapse, but in eight cases the patient specifically complained of severe pain referred to the joints. This pain was felt in one or both hip joints in six cases, and in the shoulder joint in the remaining two cases. One of these cases has been reported below because pain in the hip was the presenting feature, but in the remainder the pain occurred during the course of the disease and did not give rise to any diagnostic problem. Radiology revealed osteolytic lesions in the neighbourhoood of the joints, but in none was there collapse of the femoral head. In all these cases it was found necessary to give deep *x*-ray therapy to the region of the joint for relief of pain.

TABLE II

MUSCULO-SKELETAL MANIFESTATIONS

Total Number of Cases		46
Bone Pain	Simulating joint disease	8
	Not simulating joint disease	34
	No bone pain	4
Joint and Tendon Disease	Degenerative joint disease	3
	Gout (includes one with degenerative joint disease)	2
	Traumatic synovitis (includes one with degenerative joint disease)	2
	Para-amyloid infiltration of carpal tunnels	1
	No joint disease	40
"Brachial neuralgia"		4
Sciatica		7

Case 1, a 60-year-old electrician, was admitted to Hammersmith Hospital for radiotherapy in December, 1952. At the beginning of 1949, he had started to have treatment at another hospital for osteo-arthritis of the hips, and in March of that year he sustained a subtrochanteric fracture of his left femur through a cystic area of bone after trivial trauma. This was biopsied but showed no tumour tissue and he had been discharged wearing a caliper. In January, 1950, he began to complain of severe backache and *x* rays showed destruction of the laminae and spine of the second lumbar vertebra. He was treated with radiotherapy and subsequently had further courses, together with urethane before he died of renal failure in January, 1956.

Autopsy (Prof. C. V. Harrison) confirmed the diagnosis of myelomatosis and there were bilateral myeloma kidneys.

Bone pain seeming to arise from joints has to be distinguished from sciatica and "brachial neuralgia", which was present in seven and four cases respectively.

Diseases of the joints or tendon sheaths were present in six of the 46 cases (Table II). Only one case of para-amyloid infiltration, of the type already described, was found (Case 2); this patient had marked infiltration of both carpal tunnels 6 years after the onset of disease, and the symptoms were dramatically relieved by bilateral decompression.

There were three patients with degenerative joint disease, and two of them came under the care of the Rheumatology Unit because of their arthrosis. In these two patients it was the presence of an abnormally high erythrocyte sedimentation rate which led to the discovery of the underlying myelomatosis. A good example of this group of patients is Case 3 (described below), who showed no radiological evidence of myelomatosis for 21 months after the myeloma protein had been detected in the blood. Occult or symptomless myelomatosis has previously been reported by Osserman (1958) and by Baker and Martin (1959). Two further cases of possible occult myeloma will be described later, but as they are still under observation 3 years after the discovery of the myeloma-like protein in the peripheral blood, they cannot be included with those cases in whom the diagnosis is proven.

Acute attacks of gout occurred in two patients, one of whom also had degenerative joint disease (Case 3) and the serum uric acid rose to 16·5 mg. per cent. before she died. When the uric acid estimation was made, the blood urea level was 48 mg./100 ml. There were also two cases of

traumatic synovitis of the knee joint, but they did not present any unusual features.

Case 2, a 36-year-old woman, was first admitted to the Hammersmith Hospital in 1955 with a one-year history of low back pain. Radiography revealed vertebral collapse, and biopsy of the affected vertebra showed myeloma tissue. The symptoms improved with deep *x*-ray therapy, but further osteolytic lesions appeared in succeeding years requiring repeated courses of treatment. Bence Jones proteose was detected in 1958 and at that time the plasma proteins were 6·8 g. per cent. with no myeloma peak present on electrophoresis. In October, 1959, she complained of pain and stiffness in both shoulders, which was associated with humeral deposits.

Paraesthesiae in the median nerve distribution in both hands was first noticed in January, 1960. This gradually became more intense and was very severe during the night. During 1960 she lost 2 stone in weight and in September was re-admitted to hospital. There was marked swelling of both carpal tunnels (Fig. 1), wasting of the thenar eminences, and hypoaesthesia in the median nerve distributions. There were bilateral frozen shoulders, slight limitation of full extension of the right elbow, and a small effusion in the right knee joint. Reddish-brown cutaneous deposits were present in the upper eyelids (Fig. 2) and around the anus.

Laboratory investigations showed plasma proteins of 6·8 g. per cent., and electrophoresis showed a marked rise in the alpha-2 and beta globulins. The sternal marrow contained 20 per cent. plasma cells, many of which were immature. Serum calcium was 6·8 mEq/l., inorganic phosphate 2 mEq/l., alkaline phosphatase 7 K.A. units, serum uric acid 6·1 mg. per cent., and the blood urea 63 mg. per cent. A 24-hour urine collection contained 1,300 mg. protein/100 ml., and the congo red retention was 35 per cent. in 1 hour.

On October 7, 1960, a bilateral carpal tunnel decompression was performed with immediate relief of symptoms, and the carpal tunnel was found to be infiltrated with para-amyloid. A biopsy of a perianal cutaneous deposit also showed para-amyloid. She was treated with systemic steroids and blood transfusions and was feeling much better when discharged from hospital on November 24, 1960.

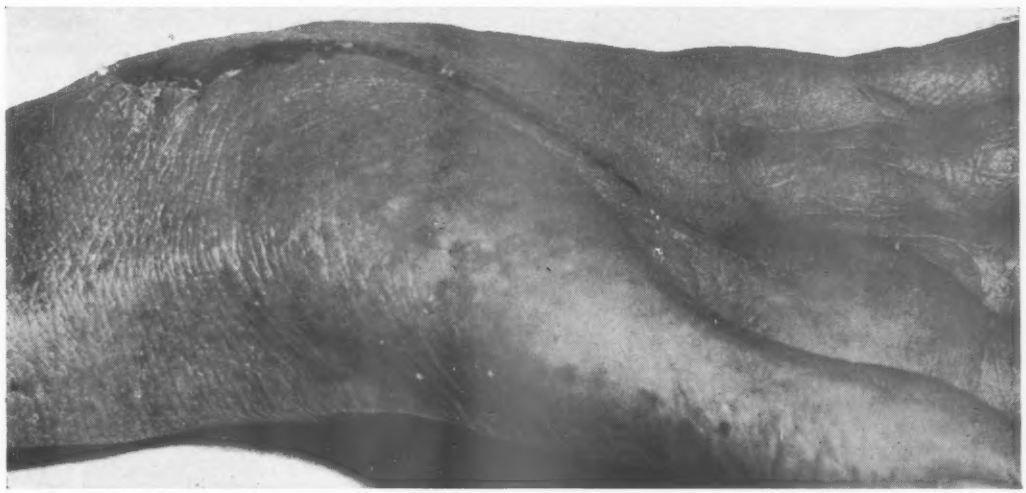


Fig. 1.—Case 2, showing swelling of carpal tunnel.

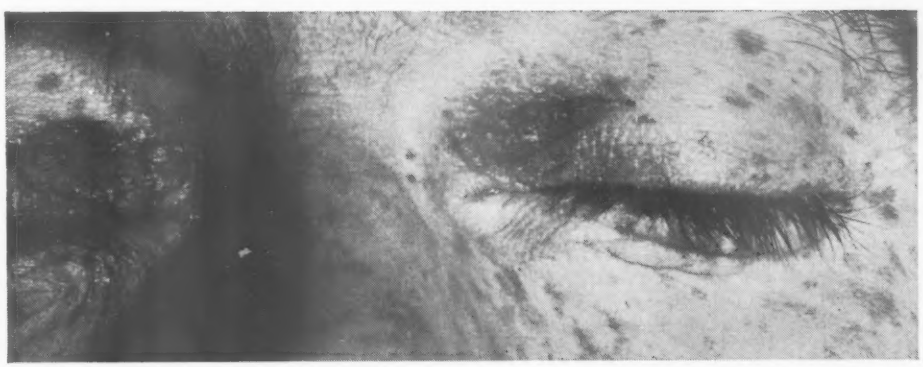


Fig. 2.—Case 2, showing amyloid deposits on upper eyelids.

Case 3, a 71-year-old widow, was first admitted to Hammersmith Hospital on June 24, 1954, with a 5-year history of pain and swelling of the knees; more recently she had had angina of effort and nocturnal orthopnoea. Examination showed an obese woman in early congestive failure with effusions in both knee joints, limited hip movement, and a blood pressure of 180/100. There was only a trace of albumin in the urine. Laboratory investigations showed an erythrocyte sedimentation rate ranging from 43 to 87 mm. in 1 hour (Westergren), a haemoglobin of 14·3 g. per cent., and a white blood count of 3,600 per c.mm., with a normal differential count. Total proteins were 8·5 g. per cent. with an albumin/globulin ratio of 4·3 : 4·2. Changes of cardiac ischaemia were seen on electrocardiography, and the chest *x* ray showed cardiac enlargement with pulmonary congestion. The cardiac failure responded to treatment, and the persistently raised sedimentation rate suggested that the arthritis might have been rheumatoid in nature despite a negative Rose-Waaler titre and the absence of erosions.

In 1955 she had a left haemarthrosis following a fall, and in August was re-admitted with severe dyspnoea. There was widespread bronchospasm, but she was not in cardiac failure. The haemoglobin had fallen to 8 g. per cent., and the erythrocyte sedimentation rate was 98 mm. in 1 hour. Electrophoresis of the plasma proteins showed a high narrow gamma globulin peak and a sternal marrow biopsy contained 60 per cent. of plasma cells. There was moderate albuminuria but no Bence Jones proteose was detected. A skeletal survey revealed no osteolytic lesions. It was decided to transfuse her, but not to treat the myelomatosis with antimitotic drugs.

In the ensuing years there were repeated admissions with anaemia and heart failure, and she suffered from recurrent chest infections. Myelomatous deposits were first detected in 1957, and in 1958 she received radiotherapy to the lumbar spine. The serum uric acid was 8·5 mg./100 ml. on November 11, 1958, and this had risen to 13·4 mg./100 ml. on March 19, 1959, when the blood urea was 48 mg./100 ml. On March 23, 1959, she developed acute gout of the terminal interphalangeal joint of the left index finger. This was incised under local anaesthesia and uric acid crystals were removed. Thereafter she remained on prophylactic colchicine, but the serum uric acid rose to 16·5 per cent. before her death. She died on April 13, 1959, from bronchopneumonia secondary to infection with an antibiotic-resistant *Pyocyaneus* organism.

The autopsy (Prof. C. V. Harrison) confirmed the diagnosis of myelomatosis and the histology of the arthritic finger joint showed deposits of urate crystals in the peri-articular tissues. The right kidney and ureter were absent, but the left kidney was macroscopically and histologically normal.

During the past 10 years six patients with protein abnormalities, in whom a definite diagnosis of myelomatosis was not reached, have been seen by the Rheumatology Unit, and these warrant detailed description. They fall into three separate groups.

(1) Two women (Cases 4 and 5) were seen in December, 1957, with a myeloma-like protein in the peripheral blood (Fig. 3, opposite), and have since been followed up; they have not developed overt myelomatosis, but the protein abnormality persists. In both cases the presence of macroglobulins was excluded by ultracentrifugation.

Case 4 had an acute arthritis of both wrist joints (Fig. 4), which on biopsy showed changes typical of rheumatoid arthritis (Fig. 5). The nature of the arthritis, which rapidly progressed to fusion of the wrist joints but has not spread to any other joints, made an infective arthritis a possibility, especially as she subsequently developed a meningococcal meningitis, but culture of the joint synovia was negative.

Case 5 was a 70-year-old nun who suffered from degenerative arthritis in the hands and cervical spine. She also complained of continual back pain, with generalized osteoporosis on radiological examination, but no localized osteolytic lesions have appeared.

(2) Two patients (Cases 6 and 7) were seen with a chronic erosive polyarthritis and macroglobulinaemia.

In Case 6 macroglobulins were detected on ultracentrifugation, and the cryocrit showed 11 per cent. cryoglobulins. The clinical features conformed to those described by Martin (1960) in his comprehensive review of 41 cases of macroglobulinaemia.

Case 7 had long-standing crippling arthritis and terminally developed pericarditis and pancytopenia, and died from massive intestinal haemorrhage. Ultracentrifuge studies were not performed on this case, but Sia's test for macroglobulins was positive and no evidence of myelomatosis was found at autopsy. The electrophoretic pattern of the plasma proteins is seen in Fig. 3 (opposite). L.E. cells were present in the peripheral blood and the Rose-Waaler titre was strongly positive, although it has been persistently negative in Case 6.

(3) Two patients (Cases 8 and 9) were seen with primary amyloidosis.

Case 8 developed myalgia, macroglossia, symptoms of bilateral carpal tunnel compression, and swelling of the knee joint, soon after making a partial recovery from acute tubular necrosis following repeated haemodialysis. It soon became apparent that there was widespread involvement with para-amyloid and he subsequently died from heart failure. At autopsy the synovia of the knee joints was stained by the congo red the patient had received in an absorption study carried out before death, and histological examination confirmed the presence of para-amyloid. Bence Jones proteose and a slight plasmacytosis in the sternal marrow were also seen in this case, but no further features of myelomatosis were detected during life or at autopsy.

Case 9 presented with symptoms of peripheral neuritis in the hands and feet, and a year later he also died of heart failure, autopsy revealing widespread para-amyloid infiltration.

Case Reports

Case 4, a 49-year-old nurse, was admitted to the Canadian Red Cross Memorial Hospital, in December, 1957. She had been in good health until 2 weeks before

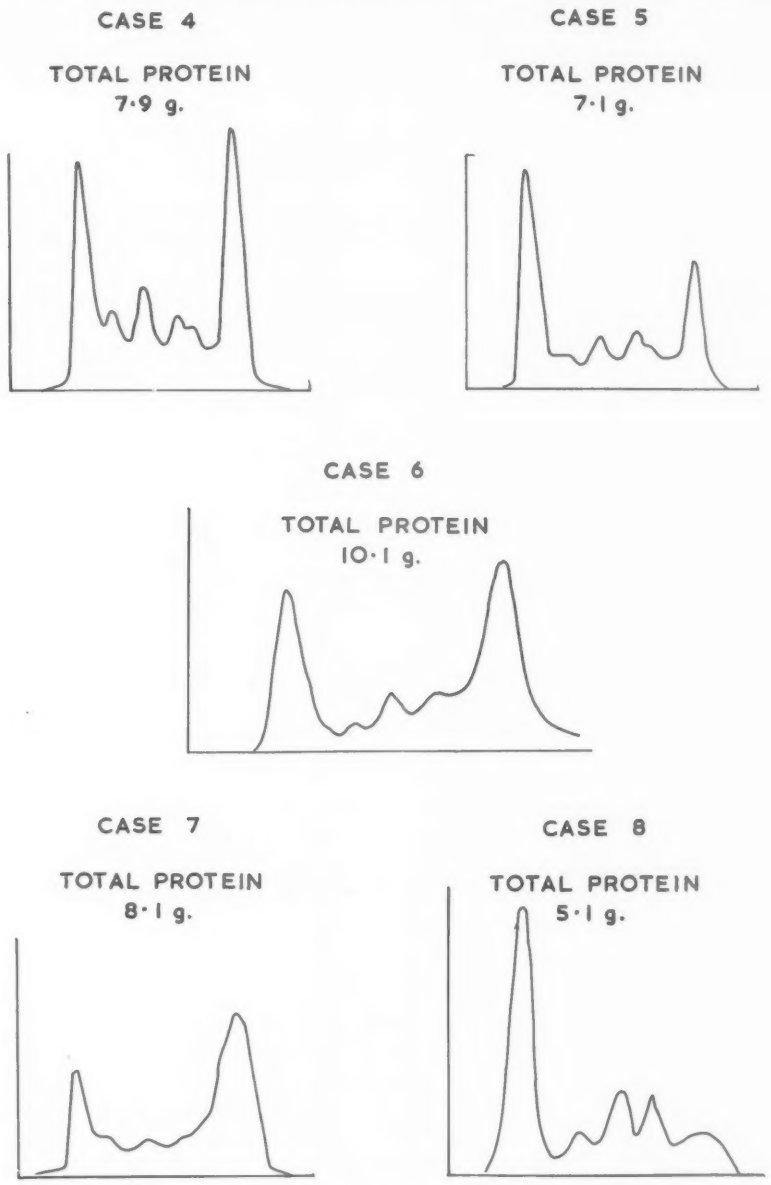


Fig. 3.—Serum electrophoresis in five cases.

admission when she had developed a sore throat and 12 days later both wrists became swollen (Fig. 4, overleaf). She had a temperature of 101° F. and both wrists were swollen, red, and very painful.

Laboratory findings included an erythrocyte sedimentation rate of 145 mm. in 1 hour (Westergren), a haematocrit of 32 per cent., and a white blood count of 10,500 per c.mm. with a normal differential count. The antistreptolysin-O titre was less than 200 units, Rose-Waaler titre 1 : 2, and latex fixation negative. Total protein was 7·9 g. per cent. and electrophoresis showed a high, narrow gamma globulin peak (Fig. 3). On ultracentrifugation there was no increase in the amount of macroglobulin, but the concentration of 7S gamma globulin was greatly increased. Marrow biopsy showed 15 per cent. of plasma cells. There was no Bence Jones proteose in the urine, and estimations of blood urea, uric acid, calcium, phosphorus, and alkaline phosphatase were all normal. *X*-ray examination showed no osteolytic lesions of myelomatosis.

She was treated with soluble aspirin 80 gr. daily for the first 5 days, but as she remained ill with a temperature rising daily to 101° F., and there was no subsidence of the arthritis in the wrists, prednisone was substituted, and this was followed by marked improvement. A synovial biopsy of the left wrist showed a histology typical of

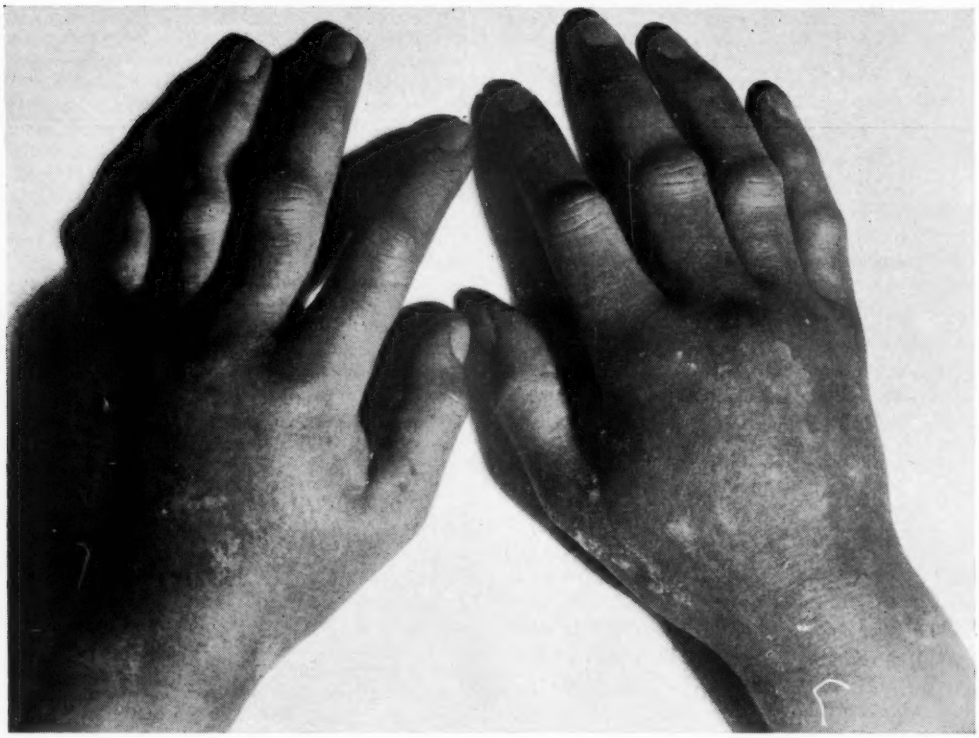


Fig. 4.—Case 4, showing acute arthritis of wrist joints.

rheumatoid arthritis (Fig. 5, opposite), and culture of the synovial membrane failed to grow organisms.

No amyloid was seen in the section and the congo red absorption was normal. Serial *x* rays showed rapid destruction of both carpi and the wrists became ankylosed (Fig. 6, opposite).

On discharge after 4 months in hospital, she still had some pain in the wrists, but was able to resume her nursing duties. Soon after discharge the Rose-Waaler titre rose to 1 : 16. The high sedimentation rate and abnormal plasma protein pattern persisted, and in October, 1959, she was admitted to another hospital with meningococcal meningitis. She made a satisfactory recovery with intensive antibiotic therapy and was well when last seen in June, 1960.

Case 5, a 70-year-old nun, was admitted to the Canadian Red Cross Memorial Hospital in December, 1957, with severe pain in the neck. She had had chronic pain in the back, neck, and hands for 30 years, and was known to have had an erythrocyte sedimentation rate of 44 mm. in 1 hour 3 years previously when she had a transitory lung infection. Examination showed some limitation of neck extension, bony swelling of the second and third metacarpophalangeal joints in both hands, and Heberden's nodes.

Laboratory findings included an erythrocyte sedimentation rate ranging from 17 to 33 mm. in 1 hour, a haematocrit of 40 per cent., and a white blood count of 7,000 c.mm., with a normal differential count. Total proteins were 7·8 g. per cent. and electrophoresis showed an abnormal gamma globulin peak (Fig. 3). No macroglobulins were detected on ultracentrifugation. There was a normal proportion of plasma cells in the sternal marrow biopsy. Estimations of blood urea, serum calcium, phosphorus, and alkaline phosphatase, and urine analysis were all normal. The Rose-Waaler titre was 1 : 2 and the latex fixation was negative. X rays confirmed the presence of degenerative joint disease in the spine and hands.

Temporary improvement of symptoms followed treatment with analgesics and physiotherapy. When last seen in 1960, she again complained of severe pain in the dorsal and cervical spine. The abnormal gamma globulin peak was still present on electrophoresis, but the urine was normal, and there were still no other laboratory or *x*-ray evidences of myelomatosis.

Case 6, a 50-year-old housewife, developed rheumatoid arthritis in 1949, and 3 years later was admitted to a chest hospital for the treatment of pulmonary tuberculosis. At this time she had erythrocyte sedimentation rates of 135 to 140 mm. in 1 hour, and after discharge began to suffer from frequent epistaxes, episodes of purpura and urticaria, and Raynaud's phenomenon.

In May, 1955, she had a series of severe epistaxes necessitating blood transfusion and was re-admitted to the chest hospital with lung field changes probably secondary to aspiration of blood, but as her sputum was again positive for acid-fast bacilli, she was given a further course of antituberculous drugs. The chest condition improved, but she was persistently anaemic with a very high erythrocyte sedimentation rate, and an abnormal serum globulin was seen to be present on electrophoresis. She was therefore transferred to Hammersmith Hospital in February, 1956.

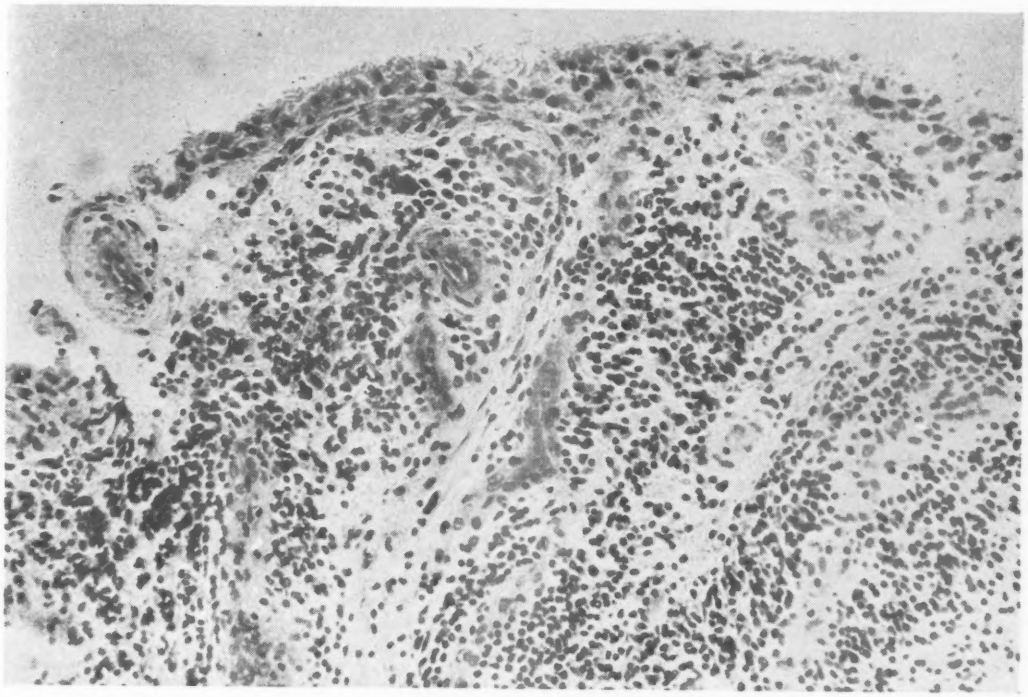
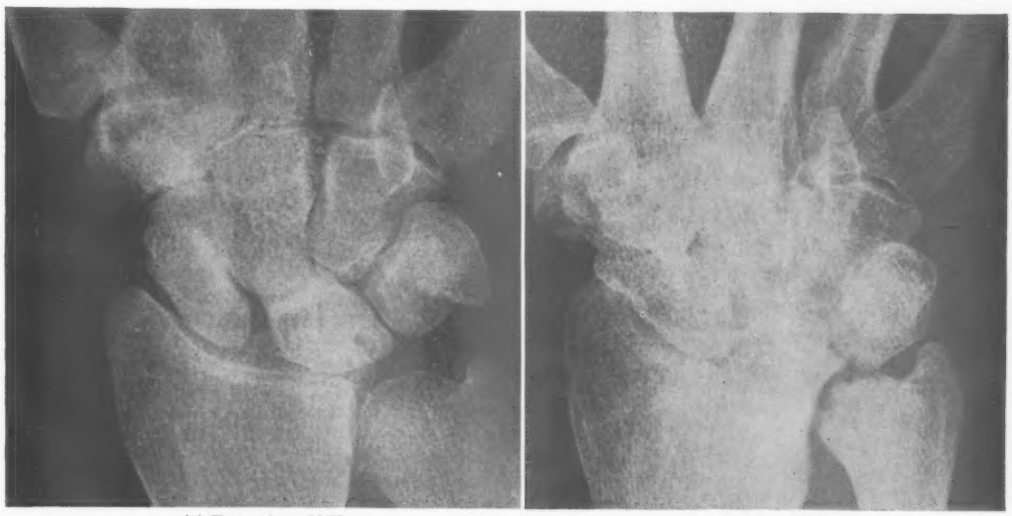


Fig. 5.—Case 4, showing biopsy of wrist joint.



(*a*) December, 1957. (*b*) July, 1958.

Fig. 6.—Case 4, showing *x* rays of left wrist.

On examination the hands and feet showed the classical deformities of rheumatoid arthritis with subluxations and erosions, but no rheumatoid nodules. Laboratory investigations showed an erythrocyte sedimentation rate of 132 mm. in 1 hour, a haemoglobin of 10·2 g. per cent., and a white blood count of 4,000 c.mm., with a normal differential count. The platelet count and prothrombin time were normal, but capillary fragility was increased. The Rose-Waaler titre, latex fixation test, and examination for L.E. cells and antinuclear factor, were all negative. The total plasma proteins were 9·8 g. per cent. with an albumin/globulin ratio of 3·2 : 6·6, and electrophoresis showed a high, narrow gamma globulin peak (Fig. 3). Macroglobulins were detected on ultracentrifugation and the cryocrit showed 11 per cent. cryoglobulins. Bence Jones proteose was not present in the urine, nor was there any albuminuria. The blood urea, serum calcium, phosphorus, and alkaline phosphatase were all normal. The sternal marrow biopsy contained 3 per cent. plasma cells. X rays showed an

erosive arthritis in the hands and feet, but there were no osteolytic lesions of myelomatosis.

On exposure to cold an extensive purpuric rash developed on both legs, and it was considered that most of the overt symptoms were due to cryoglobulinaemia. She was advised to avoid exposure to cold and discharged from hospital in November, 1956. Apart from occasional epistaxes she has remained well since her discharge and was last seen in October, 1960. Macroglobulins were still present, but cryoglobulins could not be detected.

Case 7, a 65-year-old housewife, was admitted to the Canadian Red Cross Memorial Hospital in October, 1959, with diarrhoea and vomiting. Since a cholecystectomy in 1946 she had had generalized rheumatoid arthritis which had run a progressive course necessitating numerous hospital admissions. She had never had systemic steroid therapy and had been maintained on salicylates apart from a few days on butazolidin 8 weeks before admission.

She was a pale emaciated woman, severely crippled by rheumatoid arthritis. There was epigastric tenderness, but no hepatomegaly or splenomegaly. Pressure sores were present on both buttocks.

Laboratory investigations showed an erythrocyte sedimentation rate of 143 mm. in 1 hour, a haemoglobin of 6·7 g. per cent., a haematocrit of 21 per cent., and a white blood count of 2,600 per c.mm., with 2 per cent. polymorphonuclear cells. Numerous L.E. cells were present and the serum contained the antinuclear factor. The Rose-Waaler titre was 1 : 256 and the latex fixation test was strongly positive. Total protein was 8·1 g. per cent. with an albumin/globulin ratio of 2·3 : 5·8, and electrophoresis showed a high gamma globulin peak (Fig. 3). Sia's test for macroglobulins was positive. No albuminuria or Bence Jones proteose was detected, but the blood urea was 150 mg./100 ml. The Wassermann reaction and Kahn test were negative. The electrocardiogram showed changes of pericarditis, and the *x* rays showed gross para-articular erosions of rheumatoid arthritis.

One week after admission she had a convulsion and became comatose with signs of a left hemiplegia. The following day widespread purpura appeared and she began to bleed from the gums and per rectum. She did not respond to treatment with hydrocortisone, vitamin K, blood transfusion, and tetracycline, and died within 48 hours. The autopsy (Dr. G. Loewi) showed changes typical of rheumatoid arthritis in the joints, pericarditis, and a haemorrhagic effusion in the large bowel. The bones were unusually soft and could be cut without undue exertion, and the marrow of the femur was largely of the red mottled variety. No evidence of myelomatosis or lupus erythematosus was found.

Case 8, a 39-year-old man, developed a septic bursitis of his left elbow after an injury in June, 1959, and later in the same month began to complain of headache, vomiting, breathlessness, and oliguria. He was admitted to the Royal Berkshire Hospital, where a diagnosis of acute nephritis was made, and because the blood urea was 210 mg./100 ml. he was transferred to Halton Hospital for possible haemodialysis. During his stay at Halton he was dialysed four times and it was not until the 53rd day that diuresis heralded recovery. A renal biopsy had been followed by massive haematuria necessitating removal of the kidney, and the histology showed the changes of acute tubular necrosis. By December, 1959, the blood urea had fallen to 43 mg./100 ml. and he could concentrate to S.G. 1022. In June, 1960, his blood urea was 27 mg./100 ml., but his urinary protein was 8 g./l.

He first complained of pains in the shoulders, back, and arms in April, 1960, and 2 months later he noticed soreness of the mouth and swelling of the tongue. The left knee became swollen and he had symptoms of bilateral carpal tunnel compression. Treatment with prednisone was started, with marked improvement in the pains, but the swelling of the tongue remained, and arrangements were made for him to be admitted to Hammersmith Hospital in September, 1960. There was woody swelling of the tongue and floor of the mouth with multiple small white infiltrations inside the lower lip and on the buccal mucous membrane. Small nodules were also present on the conjunctiva. The heart size was normal and a firm liver edge was felt 2 cm. below the right costal margin. A striking feature was pseudohypertrophy of the muscles of the shoulder girdle contrasting with wasting of the forearms, and there were multiple subcutaneous nodules palpable over the shoulders and back. The movement of both wrists was limited and pressure over the carpal tunnel produced paraesthesiae in the distribution of the median nerve. There was a small effusion in the left knee joint.

Laboratory investigations showed an erythrocyte sedimentation rate of 20 mm. in 1 hour (Westergren), and a white blood count of 11,000 per c.mm. The total proteins were 5·1 g. per cent. (Fig. 3). Bence Jones proteose was present, and urinary protein was 10·2 g. in 24 hours. The sternal marrow revealed an increase in plasma cells, but a skeletal *x* ray showed no osteolytic lesions typical of myelomatosis. The congo red clearance was 48 per cent. in 30 minutes, and a drill biopsy of the tongue showed amyloid infiltration.

In November, 1960, the enlargement of the tongue became more marked and the mouth was ulcerated and painful. Deep *x*-ray therapy was given to the tongue in an attempt to relieve this discomfort. At the same time his heart increased in size and he developed congestive failure, and he died at home the following month. Autopsy confirmed the presence of widespread amyloid infiltration, and of particular interest was its presence in the synovial membrane of the left knee joint which was stained by the previous congo red. The histological appearance is shown in Fig. 7 (opposite).

Case 9, a 51-year-old gardener, was first seen at the Canadian Red Cross Memorial Hospital, Taplow, in January, 1959, with a 6-month history of coldness and numbness of the toes and later of the fingers. He had also noticed weakness of the legs for several days. Until the onset of these symptoms he had been in good health. Examination revealed anaesthesia over the distal part of the feet and toes. The pulse rate was 132 with a gallop rhythm, and all the peripheral pulses were present. An electrocardiogram showed changes compatible with an old anterior infarct, with a P-R interval of 0·22 sec. Urine analysis was normal.

When next seen in July, 1959, he was complaining of hoarseness of the voice and difficulty in swallowing, and laryngoscopy revealed a smooth non-ulcerated prominence of the left false cord; a biopsy was taken, but showed no evidence of malignancy. In October, 1959, he began to have central chest pain radiating down

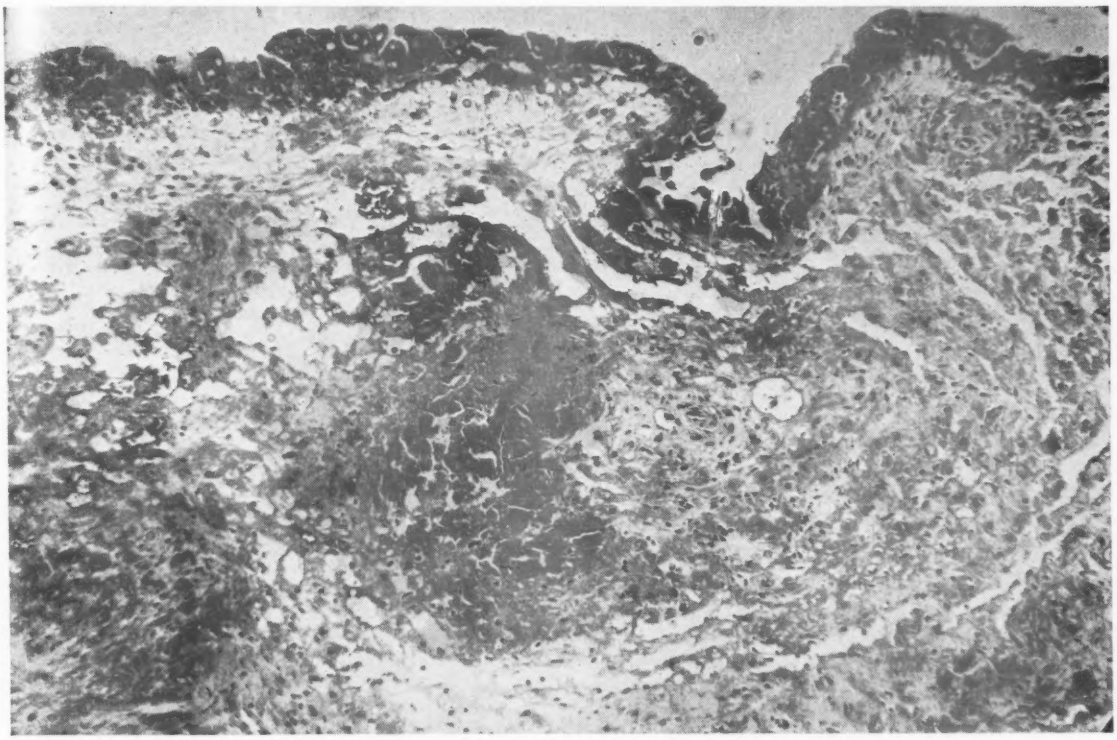


Fig. 7.—Case 8, showing autopsy section of knee joint synovium.

the left arm to the wrist; this came on when he was gardening and it was relieved by rest and trinitrin. This was followed by ankle oedema and in December, 1959, he was admitted to the Canadian Memorial Hospital with a 2-day history of diarrhoea and vomiting.

The heart was enlarged with the apex in the seventh interspace in the anterior axillary line. The jugular venous pressure was raised to the angles of the jaws, and the blood pressure was 80/60. The liver was enlarged three finger breadths below the costal margin. Signs of peripheral neuritis were present in all four limbs, and he walked with a stamping gait.

Laboratory investigations showed an erythrocyte sedimentation rate of 12 mm. in 1 hour and a haemoglobin of 12·7 g. per cent. The serum proteins were 5·39 g. per cent., with a very low gamma globulin. The sternal marrow, Wassermann reaction, and acid and alkaline phosphatases were all normal. The possibility of primary amyloidosis was considered, and on reviewing the laryngeal biopsy it was found to contain amyloid. The patient's heart failure was temporarily controlled, but he relapsed and died in February, 1960. At autopsy (Dr. D. C. Dumonde), the presence of widespread amyloid infiltration was confirmed, affecting vessel walls, muscle fibres, skin, and myocardium.

Discussion

Amyloid deposition appears to be related in some way at present undefined with proliferation of plasma cells and increased or abnormal gamma globulin. In rheumatoid arthritis there is much proliferation of plasma cells in synovial tissue, an increased number in bone marrow, and sometimes a massive packing of the spleen. Amyloid occurs in the more severe cases. It would seem possible for a somatic mutation to occur rather more frequently in these circumstances than in normal individuals, and this might possibly be the basis for the occasional occurrence of macroglobulinaemia or myelomatosis in patients with rheumatoid arthritis. Alternatively, this could be coincidence. Another possibility is that a polyarthritis of the rheumatoid type might develop in myelomatosis, of a similar nature to that which has been reported in agammaglobulinaemia (Good, Rotstein, and Mazzitello, 1957), as there is evidence that these patients have a deficiency of normal gamma globulin. Case 4 (with arthritis of both wrists) is the only one that might fall into this category; the patient had a myeloma-like protein in the peripheral blood (Fig. 3), and joint biopsy showed changes typical of rheumatoid arthritis (Fig. 5), but it should be recalled that during the course of her illness the Rose-Waaler titre rose to 1 : 16. The two cases with long-standing rheumatoid arthritis and macroglobulinaemia would appear to come into a different category, and they emphasize that

the finding of a high globulin peak on electrophoresis in a patient with polyarthritis may not necessarily be evidence of myelomatosis. The significance of macroglobulins in these patients is not known. It should, however, be mentioned that the presence of macroglobulins in myelomatosis has been reported (Adner, Wallenius, and Werner, 1960).

The development of gout in the course of some cases of myelomatosis is not unexpected, although the reports of its occurrence are few (Stewart and Weber, 1938; Davis, Weber, and Bartfeld, 1957). More difficult to explain is the para-amyloidosis which, as we have seen, can involve the joints and tendon sheaths. The borderland between primary amyloidosis and myelomatosis is shown in Case 8. This patient had swelling of the carpal tunnels and knee joint, and at autopsy the latter was found to be infiltrated with amyloid. Bence Jones proteose and a slight plasmacytosis of the sternal marrow were also seen, but otherwise he showed no features of myelomatosis, and all his symptoms were related to the widespread amyloid infiltration. This emphasizes the need to make a thorough search for myelomatosis in all cases of primary amyloidosis.

Summary

(1) The findings in 46 cases of myelomatosis seen at Hammersmith Hospital and the Canadian Red Cross Memorial Hospital, Taplow, during the 10-year period from January, 1950, to January, 1960, are reviewed, and the incidence and nature of joint involvement occurring in association with this disease have been studied.

(2) Two cases of possible occult myeloma with joint symptoms, in one of which a biopsy was indistinguishable from rheumatoid arthritis, two cases of rheumatoid arthritis with macroglobulinaemia, and two cases of primary amyloidosis are also reported. The relationship between rheumatoid-like arthritis, plasma-cell infiltration, and amyloidosis is discussed.

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Symptômes articulaires dans la myélomatose et dans des affections similaires

RÉSUMÉ

(1) On passe en revue 46 cas de myélomatose observés à *Hammersmith Hospital* et à *Canadian Red Cross Memorial Hospital*, Taplow, pendant une période de dix ans, entre janvier, 1950, et janvier, 1960, et on étudie la fréquence et la nature de l'implication articulaire associée à cette maladie.

(2) On décrit aussi deux cas de possible myélome occulte avec des symptômes articulaires, dont un, du point de vue histologique, ne se distinguait nullement de l'arthrite rhumatismale. De plus, on décrit deux cas d'arthrite rhumatismale avec macroglobulinémie et deux cas d'amyloïdose primaire. On discute le rapport entre l'arthrite du type rhumatismal, l'infiltration plasmocytaire et l'amyloïdose.

Síntomas articulares en la mielomatosis y estados similares

SUMARIO

(1) Se revisan los hallazgos en 46 casos de mielomatosis vistos en *Hammersmith Hospital* y en el *Canadian Red Cross Memorial Hospital*, Taplow, durante el período de 10 años, comprendido entre enero de 1950 y enero de 1960, y se estudia la incidencia y la naturaleza de la afectación articular asociada a esta enfermedad.

(2) Se presentan también: dos casos de posible mieloma oculto con síntomas articulares, en uno de los cuales el exámen biópsico era completamente indiferenciable del de una artritis reumatoide; dos otros casos de artritis reumatoide con macroglobulinemia y dos más casos de amiloidosis primaria. Se discute la relación entre la artritis del tipo reumatoide, la infiltración plasmocitaria y la amiloidosis.

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INTERACTIONS OF RHEUMATOID FACTOR WITH IMMUNE PRECIPITATE CONTAINING ANTIBODY OF HUMAN ORIGIN

BY

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The term "rheumatoid factor" is applied to the macroglobulin component of serum which is responsible for a group of serological reactions used as diagnostic procedures in rheumatoid arthritis.

The rheumatoid factor is able to react with antigen-antibody complexes of diverse origins. It agglutinates sheep red cells sensitized with rabbit amboceptor (Waaler, 1940; Rose, Ragan, Pearce, and Lipman, 1948), Rh-positive red cells coated with selected incomplete anti-D antibodies of human origin (Foz and Batalla, 1956; Grubb, 1956; Waller and Vaughan, 1956), and *Brucella abortus* sensitized with a strong incomplete anti-*Brucella* antibody of human origin (Foz and Batalla, 1956).

Rheumatoid factor is adsorbed on to immune precipitates consisting of various antigens and the corresponding *rabbit* antibodies (Vaughan, 1956; Edelman, Kunkel, and Franklin, 1958; Vaughan, Ellis, and Marshall, 1958; Corcos, 1960; Mellors, Nowoslawski, Korngold, and Sengson, 1961). Vaughan (1956) observed that absorption with an immune precipitate consisting of diphtheria toxin and *human* antitoxin did not reduce the activity of one rheumatoid serum in the Waaler-Rose test. Under the experimental conditions, a considerable solubility of the precipitate made the quantitative data uninterpretable. Additional data were not available in the literature concerning reactions of rheumatoid sera with immune precipitates containing antibody of human origin.

Recently, we have had the opportunity of studying a strong human precipitin and its reactions with rheumatoid sera. The present paper describes the results of these experiments. After completion of the experiments, we learned of the independent investigations of Aho, Kirpilä, Wager, and Virkkunen (1961) which confirm and extend our findings.

Materials and Methods

Precipitating Antibody.—The antibody was found by Dr. S. Blix during studies on fibrinolysis. Its properties are described in another paper (Blix, 1961), and only a few data will be given here.

The patient R.K., a 58-year-old male, had a 5-year history of peripheral arterial insufficiency in both legs. Bilateral femoral-popliteal by-pass operations had been performed and were followed by secondary thrombosis with purulent ulcerations. These were treated locally with Varidase* eight times during the first 6 months of 1960, and the antibody was demonstrated in November, 1960.

The present experiments were performed with serum samples obtained on different occasions in December, 1960, and January, 1961, and the antibody activity decreased slowly during this period. After chromatography on DEAE-cellulose (kindly performed by Dr. T. Reinskou), it was demonstrated by Dr. Blix that antibody activity was present in the fractions containing 7S γ-globulin. The patient was of type Gm(a+ b+ x+). The serum titre was less than 1 : 5 in the Waaler-Rose test and the F.II latex particle test was negative.

Tests for Rheumatoid Factor Activities

Waaler-Rose Test.—This was made with human Group O Rh-negative red cells (Podliachouk, Eyquem, and Jacqueline, 1958), using the corresponding amboceptor from rabbits (commercial preparation, Institut Pasteur, Paris, France). The sensitizing amboceptor was used in one-quarter of the minimum agglutinating dose.

F.II Latex†-Particle Test.—This was performed according to Winblad (1960, and personal communication) with the following slight modifications: the suspension was stabilized with human albumin, and 0·15 M

* *Varidase* was the commercial preparation of Lederle, New York, N.Y., Lots No. 2201-108A and 2200-982A.

† *Akryl* plast particles (Latex) were kindly provided by AB Bofors, Nobelkrut, Bofors, Sweden.

Sigma buffer pH 8·2 was used. To 0·5 ml. serum dilution was added 0·5 ml. suspension of γ-globulin-coated particles; the results were read macroscopically without centrifugation after sedimentation overnight at 37° C.

Agglutination Tests with Red Cells Coated with Incomplete Anti-D.—These were made on slides as previously described (Harboe, 1959, 1960a). Rheumatoid sera containing anti-Gm(a) and anti-Gm(x) (Grubb, 1961a) were selected from the panel of sera used for Gm-typing in this laboratory. Anti-D R.A. was used to coat red cells for determination of Gm(a) and Gm(x) types. Titres of anti-Gm(a) and anti-Gm(x) are given as the titres of sera known to contain these substances, when investigated with red cells coated with anti-D R.A. Anti-D S.V. was used for Gm(b) typing.

Red cells coated with anti-D Mu. and Ri. are known to be agglutinated by nearly all rheumatoid sera showing positive Waaler-Rose and F.II latex-particle tests. Since these anti-D sera may be used diagnostically for the demonstration of rheumatoid factor activity, they are referred to as "diagnostic anti-D" in this paper. The antibodies are described in more detail elsewhere (Harboe, 1960b).

Absorption Procedure.—One ml. serum from the patient R.K. was incubated with 1 ml. of a solution of Varidase containing 10,000 units/ml. for 1 hr at 37° C. and 20 hrs at 4° C. Preliminary experiments indicated that these concentrations corresponded to the equivalence point of the precipitation curve. The precipitate was isolated by centrifugation for 30 min. at 1,800 G, and washed three times in 10 ml. chilled saline. The washed precipitate (containing about 0·12 mg. nitrogen as determined by micro-Kjeldahl analysis) was used to absorb 2 ml. rheumatoid serum diluted 1 : 5 for 24 hrs at 4° C. The absorption was performed in sealed tubes during continuous slow movement to secure optimal contact between precipitate and serum. After absorption, the precipitate was removed by centrifugation and the supernatant transferred to a second tube for repeated absorption. The procedure was repeated for a different number of times, as indicated in the text. After the final absorption, the supernatant was tested for rheumatoid factor activities as indicated. For control, other portions of the rheumatoid sera diluted 1 : 5 were treated in exactly the same way, except that no precipitate was added. In most sera, a spontaneous precipitate formed within a few days and was removed during centrifugation. For additional control, a third tube of each diluted rheumatoid serum was frozen down (−25° C.) at the beginning of the absorption procedure. The tubes were thawed at the end of the absorption procedure and tested simultaneously with the other materials. Spontaneous precipitates are known to contain rheumatoid factor (Christian, 1959), but there was no significant difference in activity between the frozen samples and the samples which were kept at 4° C.

Quantitation of Precipitated Protein.*—To 0·75 ml. serum R.K. was added 0·75 ml. Varidase containing 20,000 units/ml. This concentration of approximately two times equivalence was chosen on the basis of data from Edelman, Kunkel, and Franklin (1958). The mixture was incubated for 1 hr at 37° C. before the addition of 0·75 Ul. rheumatoid serum A.H. or normal sera showing negative Waaler-Rose and F.II latex-particle tests for control. After additional incubation for 20 hrs at 4° C., the precipitates were spun down by centrifugation for 60 min. at 1,800 G at 4° C. The supernatants were carefully removed and the precipitates washed twice in chilled saline. Finally, the precipitates were dissolved in 4 ml. 30 per cent. urea in 0·2 N NaOH, and the optical density was determined at 280 mμ in a Beckman spectrophotometer, model DU-G2400.

Experiments and Results

Serological Activities before and after Absorption.—The Figure (opposite) shows the results of absorption experiments on a rheumatoid serum (198/LW) containing anti-Gm(a). After one absorption, anti-Gm(a) activity could no longer be demonstrated, nor were cells coated with "diagnostic" anti-D Ri. agglutinated. The titres in the Waaler-Rose and F.II latex-particle tests were also reduced, but to a less degree.

The Figure also shows that another rheumatoid serum (270/AA), which also contained anti-Gm(a), gave similar results.

Serum S.V. contained anti-Gm(x) with a titre of 1 : 640. After one absorption with the immune precipitate, no anti-Gm(x) activity could be demonstrated.

Two rheumatoid sera with fairly strong serological reactions, which did not agglutinate red cells coated with anti-D R.A., were then investigated. The serum titre was determined after four times absorption with the immune precipitate in the Waaler-Rose test and F.II latex-particle test, and against red cells coated with "diagnostic" anti-D Mu. and Ri., and compared with the unabsorbed control.

Table I (opposite) shows that there was a marked reduction in all serological activities by the absorption procedure.

Quantitative Studies.—The results of one experiment are shown in Table II (opposite). It may be seen that the amount of precipitated protein was greater when

* *Protein Preparations.*—Pooled human γ-globulin was the commercial preparation of AB Kabi, Stockholm, Sweden, Batch No. 70318. Human albumin was the commercial preparation of AB Kabi, Batch No. 67103.

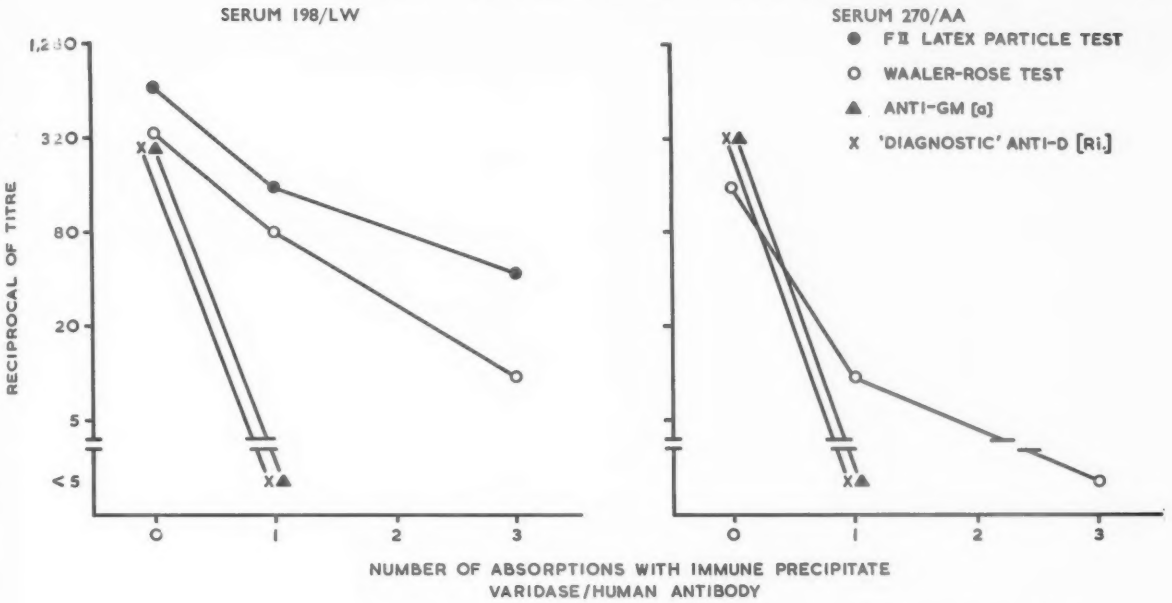

Figure.—Absorption of rheumatoid serum 198/LW and 270/AA containing anti-Gm(a) with human specific precipitate.

TABLE I

ABSORPTION OF RHEUMATOID SERA WITH HUMAN SPECIFIC PRECIPITATE

Reciprocals of titres in each different test before and after four times absorption are given

Test		Waaler-Rose		F.II-Latex Particle		"Diagnostic" Anti-D Sera			
						Anti-D Mu.		Anti-D Ri.	
		Before	After	Before	After	Before	After	Before	After
Serum ..	A.H.	320	5	1,280	<5	640	<5	320	<5
	O.H.	320	20	2,560	20	320	<5	320	<5

TABLE II

QUANTITATION OF PRECIPITATED PROTEIN

For technique of investigation, see text

Reagents Incubated				Optical Density (280 mμ) of Dissolved Precipitate
Varidase		Serum R.K.	Saline	0·120
Varidase		Serum R.K.	Normal Serum 1	0·120
Varidase		Serum R.K.	Normal Serum 2	0·138
Varidase		Serum R.K.	Rheumatoid Serum A.H.	0·200
Varidase		Serum R.K.	Rheumatoid Serum A.H.	0·210
Controls ..	Varidase	Saline	Saline	0
	Saline	Serum R.K.	Saline	0
	Saline	Saline	Rheumatoid Serum A.H.	0·010
	Saline	Saline	Normal Serum 1	0
	Saline	Saline	Normal Serum 2	0
	Varidase	Saline	Rheumatoid Serum A.H.	0
	Saline	Serum R.K.	Rheumatoid Serum A.H.	0

the immune precipitate was incubated with rheumatoid serum A.H. than after incubation with control sera showing negative tests for rheumatoid factor or saline. These findings were reproduced on three occasions. The experiment was made with only one rheumatoid serum (A.H.) because, as purified rheumatoid factor was not available, the tests had to be carried out with neat rheumatoid serum. Under these conditions, spontaneous precipitation (Christian, 1959) often makes interpretation difficult or impossible. Serum A.H. was selected because it was the only one, in a series of rheumatoid sera with fairly strong serological reactions, which gave only a trace of spontaneous precipitate after dilution 1 : 5 in saline and several days' storage at 4° C. Relevant controls are included in the Table.

Controls

(1) Varidase is a purified preparation of the streptococcal enzymes streptokinase and streptodornase. Streptokinase activates the fibrinolytic system of human plasma and serum resulting in formation of plasmin (fibrinolysin) which is a proteolytic enzyme. In the organism, the activity of plasmin is directed primarily towards fibrin and, to some extent, fibrinogen. In addition, it may digest other proteins (Sherry, Fletcher, and Alkjaersig, 1959), possibly including the macroglobulins responsible for the activity in the present serological tests.

Four rheumatoid sera were incubated with Varidase under conditions optimal for plasmin formation (Blix, 1961). No reduction of serological activity was observed in the sera when compared with similar incubation with saline for control.

(2) Serum R.K. was of type Gm(a+). During the absorption procedure, Gm(a+) γ-globulin might therefore loosen from the immune precipitate in amounts sufficient to inhibit anti-Gm(a). After absorption of serum 198/LW (Figure), the following experiments were made to study this possibility:

To demonstrate the presence of Gm(a+) γ-globulin, we used anti-Gm(a) Kouba and red cells coated with anti-D R.A. In this system, Gm(a+) normal serum showed full inhibition of agglutination in dilutions up to 1 : 1,280, whereas Gm(a−) normal serum did not inhibit in dilution 1 : 5. After three times absorption of serum 198/LW with the immune precipitate, dilution 1 : 5 had a definite inhibiting ability towards serum Kouba. At dilution 1 : 10, no inhibition was observed. The unabsorbed control of serum 198/LW did not inhibit in dilution 1 : 5 or higher—the latter experiment was performed after heating of diluted serum 198/LW to abolish its agglutinating ability (Grubb and Laurell, 1956; Harboe, 1960a). The results of the experiments are summarized in Table III.

TABLE III

ATTEMPT TO DEMONSTRATE Gm(a+) GAMMA-GLOBULIN LOOSENED FROM SPECIFIC PRECIPITATE DURING ABSORPTION

Reagents: Anti-Gm(a) Kouba 1 : 8, red cells coated with anti-D R.A. Degree of agglutination recorded from ++++ to − (*cf.* Harboe, 1960a)

Dilution of Test Material	Test Material			
	198/LW		Gm(a−)	Gm(a+)
	Before Absorption*	After Absorption	Control	Control
1 : 5	++++	+	++++	−
1 : 10	++++	+++	++++	−
1 : 20	++++	++++	++++	−
1 : 40	++++	++++	++++	−
1 : 80	++++	++++	++++	−
1 : 160	++++	++++	++++	−
1 : 320	++++	++++	++++	−
1 : 640	++++	++++	++++	−
1 : 1280	++++	++++	++++	+
1 : 2560	++++	++++	++++	+++
1 : 5120	++++	++++	++++	++++

Controls: Anti-Gm(a) Kouba 1 : 8 and coated cells: ++++
Anti-Gm(a) Kouba 1 : 8 and uncoated cells: −
Saline and coated cells: −
All test materials and coated cells: −

* Serum 198/LW diluted 1 : 5 and heated at 65° C. for 10 min. before testing (Grubb and Laurell, 1956; Harboe, 1960a).

After absorption of serum 270/AA (Figure), similar experiments were made with virtually identical findings. It was concluded that a minimal amount of Gm(a+) γ-globulin loosened from the immune precipitate under the experimental conditions. The amount was too small to abolish the anti-Gm(a) activity of the serum which was absorbed.

(3) Absorption of rheumatoid sera with immune precipitates consisting of various antigens and the corresponding rabbit antibodies may abolish serological activity in the Waaler-Rose test leaving the latex-fixation titres virtually unchanged. Corcos (1960) found that this was the case when human albumin or purified 7S human γ-globulin was used as antigen in the immune precipitate. He also found that immune precipitates containing aggregated human γ-globulin removed the activity in both serological tests, as does absorption with aggregated human γ-globulin alone. An important source of error in the present experiments might therefore be that the antigen itself, Varidase, might react with the rheumatoid factor. Inhibition experiments were made to clarify this point:

Four rheumatoid sera were diluted until they contained ten agglutinating doses in the different tests, and serial two-fold dilutions of a Varidase solution originally containing 10,000 units/ml. were added in order to test for inhibiting capacity. In the Waaler-Rose test, no

significant inhibition was found. In the F.II latex-particle test, slight inhibition was observed in the first two tubes. Anti-Gm(a) Kouba and 198/LW were not inhibited by Varidase (these experiments were performed using red cells coated with anti-D G63, see below). Whether the agglutination of red cells coated with anti-D Ri. was inhibited by Varidase, could not be tested because it was found that the preparation agglutinated such cells.

Rh-positive red cells were coated with ten different strong incomplete anti-D sera and tested for agglutination by serial dilutions of a Varidase solution originally containing 10,000 units/ml. Red cells coated with one anti-D serum (G63) were only weakly agglutinated in a narrow concentration range of Varidase, while cells coated with any of the other anti-D antibodies were strongly agglutinated. A "prozone phenomenon" was observed with six of the anti-D antibodies; no agglutination was observed by the highest concentrations of Varidase, whereas lower concentrations of the preparation showed strong agglutinating ability. The basic nature of this agglutination is unknown. It is probably not of enzymic nature, as the activity was somewhat stronger at 4° C. than at 37° C. The agglutination was inhibited by low concentrations of both human albumin and γ-globulin.

It was concluded from these experiments that Varidase itself did not inhibit the rheumatoid factor to a significant degree and, accordingly, that such inhibition could not explain the findings of the absorption experiments.

Discussion

The rheumatoid factor is able to react with γ-globulin of diverse origins. Theoretically of great importance is whether it can react with human γ-globulin *in vivo*, and whether this reaction is of any pathophysiological consequence for the individual.

Experiments in this laboratory (Harboe, 1961) indicate that anti-Gm(a) is a separate component of the complex of closely related macroglobulins usually designated as rheumatoid factors. Anti-Gm(a) and the other specific agglutinating substances of the Gm system are inhibited by native human 7S γ-globulin (Grubb, 1961b). Similar reactions are directly observed in experiments using red cells coated with selected incomplete anti-D antibodies, where prozones often occur in agglutination tests. It has been demonstrated that these prozones are frequently caused by the simultaneous presence of an agglutinating substance and its specific inhibitor in individual rheumatoid sera (Swahn and Grubb, 1958; Harboe, 1960a). Additional evidence for a reaction between rheumatoid factor and human γ-globulin *in vivo* is the presence of the 22S complex in some rheumatoid sera. Rheumatoid factor is composed of 19S γ-globulins which often exist in the circulation bound to 7S γ-globulin, and this complex has a sedimentation coefficient of 22S (Franklin, Kunkel, Müller-Eberhard, and Holman, 1957).

At the beginning of the experiments described in this paper, the behaviour of rheumatoid factor with immune precipitates containing antibody of human origin was scarcely known. The only data available were those on rheumatoid serum S.H., which was absorbed by Vaughan (1956) with a precipitate consisting of diphtheria toxin and human antitoxin. There was no reduction in activity after absorption as judged by the Waaler-Rose test. The reasons for the discrepancy between Vaughan's findings and ours are probably that we did repeated absorptions, whereas his serum appears to have been absorbed only once, and that the other tests (demonstration of anti-Gm(a) and agglutination of red cells coated with "diagnostic" anti-D) are more sensitive than the Waaler-Rose test (Figure). The present findings showed that different components of the rheumatoid factor were adsorbed on to the specific precipitate containing human antibody.

After completing the present investigations, we learned of the important paper of Aho, Kirpilä, Wager, and Virkkunen (1961). They immunized two patients with rheumatoid arthritis, who had strongly positive serological reactions, with diphtheria toxoid, and both patients developed strong precipitating antibodies. It was found that rheumatoid factor was adsorbed to, and could be eluted from, the precipitates, which consisted of diphtheria toxoid and the patients' own antitoxins. Identical findings were made by three different tests for rheumatoid factor activity: the Waaler-Rose test, the F.II latex-particle test, and an agglutination test with red cells coated with anti-D Ri.

Studies on the Gm system have shown that components of the rheumatoid factor may react with the individual's own native γ-globulin (Swahn and Grubb, 1958; Harboe, 1960a). The present experiments show that the rheumatoid factor is adsorbed on to immune precipitate containing antibody of human origin. The experiments of Aho, Kirpilä, Wager, and Virkkunen (1961) further demonstrate that immune complexes containing precipitating antibody from rheumatoid arthritis patients react with their own rheumatoid factor. It remains to be demonstrated whether these phenomena observed *in vitro* may indicate autoimmune mechanisms in rheumatoid arthritis.

Summary

The behaviour of rheumatoid factor was studied with an immune precipitate consisting of "Varidase" and a human 7S γ-globulin antibody. Different

components of rheumatoid factor [as defined by the Waaler-Rose test, F.II latex-particle test, agglutination tests with red cells coated with "diagnostic" anti-D, and demonstration of anti-Gm(a) and anti-Gm(x)] were all absorbed on to this immune precipitate.

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Interactions du facteur rhumatismal avec un immun-précipité contenant des anticorps d'origine humaine

RÉSUMÉ

On étudia le comportement du facteur rhumatismal avec un immun-précipité consistant de "Varidase" et d'un anticorps humain, la globuline gamma 7S. De différents composants du facteur rhumatismal—définis par la réaction de Waaler-Rose, la réaction F.II d'agglutination de particules de latex, des réactions d'agglutination des globules rouges enduites d'anti-D "diagnostique" et mise en évidence d'anti-Gm(a) et anti-Gm(x)—furent tous absorbés dans ce immun-précipité.

Interacciones del factor reumatoide con un inmune-precipitado conteniendo anticuerpos de origen humano

SUMARIO

Se estudió el comportamiento del factor reumatoide con un inmune-precipitado conteniendo "Varidase" y un anticuerpo humano, la globulina gamma 7S. Diferentes compuestos del factor reumatoide—definidos por la reacción de Waaler-Rose, la reacción F.II de aglutinación de partículas de latex, reacciones de aglutinación de eritrocitos cubiertos de anti-D diagnóstico y comprobación de anti-Gm(a) y anti-Gm(x)—fueron todos absortos en este inmune-precipitado.

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STUDIES ON THE ISOLATION OF RHEUMATOID FACTOR

BY

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The need for the isolation of rheumatoid factor in a high state of purity and in sufficient quantity for antiserum production has led to an appraisal of the various purification methods available.

Ziff, Brown, Lospalluto, Badin, and McEwen (1956) demonstrated that the sensitized sheep cell agglutinating activity of rheumatoid serum was precipitated in the euglobulin fraction, and Svartz and Schlossmann (1954) showed that this factor precipitated in the "cold globulin" fraction and were thus able to obtain a serologically active but heterogenous concentrate.

Later, both these groups of workers applied the cellulose ion exchange resins, diethylaminoethyl and carboyxmethyl cellulose, developed by Peterson and Sober (1956) to further fractionate euglobulin fractions (Lospalluto and Ziff, 1959; Svartz, Carlson, Schlossmann, and Ehrenberg, 1958).

Ultracentrifugal studies of rheumatoid sera and euglobulin fractions showed that the factor circulated as a high molecular weight component of sedimentation coefficient 19 or 22S and this property has been used by Kunkel, Franklin, and Muller-Eberhard (1959) and Heimer, Federico, and Freyberg (1958) to separate rheumatoid factor from lower molecular weight proteins. Most of these workers were able to obtain reasonably pure 19S globulin with a considerable concentration of serological activity. In these investigations, however, little attention was paid to immunochemical analyses of individual proteins, and the relative merits in each step in the concentration of rheumatoid factor were not determined.

In the investigations now reported, an attempt has been made to determine the most efficient procedure available for the isolation of rheumatoid factor in a relatively pure form. The recovery of rheumatoid factor activity has been measured after each procedure by the Rose-Waaler sensitized sheep cell technique, and the fractionation achieved has been assessed by total protein estimation, ultracentrifugal, immunochemical, and immuno-electrophoretic analyses. In this way it has been possible to make a critical comparison of the effectiveness and deficiencies of the different methods of purification. These methods included euglobulin precipitation to obtain a crude concentrate of rheumatoid factor, followed by diethylaminoethyl cellulose chromatography, zone centrifugation, and Cohn low-temperature ethanol fractionations in various orders and combinations.

Some of the difficulties encountered are discussed below; they include serious loss of serological activity as well as low degree of isolation in some protein preparations.

Materials and Methods

Rheumatoid Sera

Sera were obtained from ten patients with classical active rheumatoid disease, selected because they had the highest Rose-Waaler sensitized sheep cell agglutination titre of those available at the time; this titre ranged between 1/1,024 and 1/5,000 in half the patients; exceptionally a serum with a titre as low as 1/64 or as high as 1/12,600 had to be used. There were seven male and three female patients, aged 40 to 67 years, with a 4 to 32-year history of rheumatoid arthritis.

Estimation of Protein Concentration

The modification of the Folin-Ciocalteau method developed by Lowry, Rosebrough, Farr, and Randall (1951) was usually employed, using a bovine serum albumin standard.

Measurement of Rheumatoid Factor Activity

The rheumatoid factor was assayed by Ball's modification of the sensitized sheep cell agglutination test of Rose-Waaler (Ball, 1950), but using one-third of an

* In receipt of a Medical Research Council Studentship for training in research methods.

agglutinating dose for sensitization and studying the pattern of sedimentation in plastic cups as the index of agglutination. Units of serological activity have been calculated by multiplying the volume of the sample by the reciprocal of its Rose-Waaler titre. Specific activities are derived by dividing the reciprocal of the Rose-Waaler titre by the protein concentration in mg./ml. and is equivalent to the maximum volume (ml.) to which 1 mg. protein can be diluted and still give a positive Rose-Waaler titre.

Euglobulin Precipitation

Crude protein precipitates rich in rheumatoid factor activity were obtained by lowering the ionic strength of the serum in various ways, involving dilution with, or dialysis against, water (as described in Table III). On two occasions precipitation with 33 per cent. saturated ammonium sulphate was used after failure to precipitate rheumatoid factor activity by dialysis.

Ion Exchange Chromatography

Chromatography in columns (20 cm. high, 1·1 cm. diameter) of DEAE cellulose, prepared according to the method described by Peterson and Sober (1956), was performed by step-wise elution in a manner essentially similar to that employed by those workers (Sober, Gutter, Wyckoff, and Peterson, 1956). DEAE cellulose chromatography was preferred to chromatography on carboxymethyl cellulose (CM), as applied by Fallet, Lospalluto, and Ziff (1958), because of the superior resolving power of the former method in relation to 19Sγ globulin.*

In some cases, however, 0·05 M NaH_2PO_4 solution containing 0·15 M NaCl was used as a final eluent in order to remove the 19S γ globulin in a sharp band.

"Batch" chromatography on DEAE cellulose was carried out by a modification of the method recently described by Stanworth (1960), using filtration instead of centrifugation and with suitable washing (pH greater than 5 and ionic strength 0·05 M) and eluting solutions (1·5 M NaCl).

Cohn Low-temperature Ethanol Fractionation

A small-scale fractionation procedure designed to use 5-ml. volumes of plasma was employed. This was a modification of "Method 10" of Lever, Gurd, Uroma, Brown, Barnes, Schmid, and Schultz (1951), developed by Dr. K. W. Walton. It involved the adjustment of the pH of the sample to 7·4 with 0·01 M NaOH before the initial precipitation, and it provided a rapid means of separating the γ-globulins from other serum protein constituents.

* This is the high molecular weight component of normal serum which is associated with iso-agglutinin activity and is termed B_2M by Grabar and Williams (1955), on the basis of the position of its precipitin line in the serum immuno-electrophoretic pattern. Other synonyms include the term "Iota" protein used by Stanworth (1959) and the γ_1 macroglobulin described by Kunkel (1960). In this paper it will be constantly referred to as 19S γ; it is not suggested that it is identical with rheumatoid factor.

Zone Centrifugation

Fractionations by this procedure were achieved by centrifuging 1-ml. samples in buffered sucrose gradients in lusteroid tubes (5-ml. capacity) at 39,000 r.p.m. and 12·5° C. in a Spinco SW 39 rotor for 7 hrs. This is a modification of the method used by Kunkel and others (1959) in the fractionation of 19S serum proteins (Stanworth, James, and Squire, 1961). Spinco No. 40 angle rotors were also used on two occasions.

Analytical Ultracentrifugation

Analyses were carried out in 12-mm. cells in a Spinco Model E machine at 60,000 r.p.m. and 20° C. Samples (1-ml.) were pre-dialysed for 16 hrs against 1 L. barbitone buffer (pH 8·6; I = 0·05) containing 0·2 M NaCl, or phosphate buffer pH 6·9; M = 0·06 + 15 M NaCl.

Concentration of Protein Solutions

Details of the ultrafiltration and carbowax (polyethylene glycol) methods used are given in Table VI.

Quantitative Gel-diffusion Precipitin Analysis

Estimations were carried out by Dr. J. F. Soothill, using the technique developed by Gell (1957). Three specific antisera were used. One was against 7S γ globulin, and one against high molecular weight α_2 glycoprotein (α_2 macroglobulin of Kunkel). The one against 19S γ globulin was raised with a macroglobulin from the serum of a patient with macroglobulinaemia and was absorbed with 7S γ globulin and hypogammaglobulinaemic serum; this antiserum successfully measures 19S γ globulin. Further details of these antisera are reported by Soothill (to be published). The results for 7S γ are obtained as mg./100 ml. The results for the other two proteins were obtained as a percentage of the concentration in a standard serum from a healthy adult male. For calculation purposes, arbitrary conversion factors to mg./100 ml. were used. These are 100 per cent. α_2 = 100 mg./ml., and 100 per cent. 19S γ = 50 mg./ml.

Immuno-electrophoresis

Analyses were carried out in buffered agar according to the technique of Grabar and Williams (1955).

Results

The properties of the ten rheumatoid sera used for serial fractionation procedures are shown in Table I (opposite).

As already mentioned, the Rose-Waaler titres were variable, so that the specific activity also varied from 1·8 to 146 ml./mg. In Table I the compositions of these sera are also shown in terms of ultracentrifugal and immunological analyses; these are given mainly for comparison with the

TABLE I

PROPERTIES OF RHEUMATOID SERA USED

Case No.	Sex	Protein Concentration (mg./100 ml.)	Specific Activity (ml.‡/mg.)	Ultracentrifugal Composition (mg./100 ml.)					Immunological Composition (mg./100 ml.)		
				22S	19S	10S	7S	4·5S	α_2*	19S γ*	7S γ
1	F	3,700†	1·8	—	130	—	840	2,730	Not determined		
2	F	7,700	9·4	—	150	—	420	7,130	Not determined		
3	M	7,800	106	80	170	120	730	6,700	56	100	750
4	M	7,500	6·8	—	135	—	900	6,460	88	150	960
5	F	10,900	24	—	390	—	1,910	8,600	200	200	4,480
6	M	8,100	63	—	100	—	1,000	7,000	75	60	1,280
7	M	7,700	33	110	180	—	670	6,740	150	150	1,920
8	M	9,200	14	—	250	110	2,700	6,170	75	300	2,560
9	M	8,750	146	450	340	—	1,200	6,760	150	125	1,120
10	M	8,800	36·4	105	105	650	1,350	6,690	200	500	1,280
S.D. Rheumatoid		8,500±1,080			202±107		1,220±700	6,900±690	124±52	198±184	1,794±390
S.D. Normal ..					170±56		1,170±290	6,070±300	107±26	71±30	1,240±250

* See p. 370.
† Serum from Case 1 had been diluted before use.
‡ Specific Activity = Reciprocal Rose-Waaler Titre ÷ Protein Concentration (mg./100 ml.) = (ml./mg.) (see p. 370).
S.D. = Standard Deviation (excluding Serum 1 in the rheumatoid results).
Normal Serum: Ultracentrifugal results from eleven normal sera and average protein content at 7 g. per cent. assumed. Immunological results from twenty normal sera.

composition of products, but it may be noted that there is a general tendency for raised levels of total 7S and 7S γ and probably of 19S γ globulins and high molecular weight α_2 glycoproteins.

Full-scale fractionations were undertaken on ten rheumatoid sera, as summarized in Table II (overleaf), the ninth and tenth being undertaken after a full study of the results of the first eight. Considering Runs 1 to 8, gains in specific activity have been from only 3- to 29-fold (excluding Run 6). Since the rheumatoid factor is a 19S protein, which, even in the serum with highest Rose-Waaler titre, only contributes 4 per cent. of the total protein, it could be expected that efficient zone centrifugation alone would give a 25-fold increase in specific activity and a "pure" 19S protein. However, as will be discussed later, efficient zone centrifugation of 20 to 100 ml. serum is not a practical proposition with the apparatus at our disposal, so some prior method of removing the bulk of contaminating proteins is advantageous.

The recovery of units has varied from 1 to 50 per cent., being below 15 per cent. in any procedure using column chromatography on DEAE cellulose. The final product constituted between 0·11 and 3 per cent. of the starting protein. If the recovery of units had been higher these results would have been more satisfactory. The yield of final product lay between 5 and 30 mg. except in Runs 3 and 7 (only a small-scale fractionation).

Only two preparations were judged free of 7S protein by ultracentrifugal analysis, and these had traces of 7S γ as measured by the very sensitive immunological technique (Runs 3 and 8).

The concentrations of activity obtained in Runs 1 to 8 could quite possibly have been achieved by an efficient euglobulin precipitation with subsequent zone ultracentrifugation, and judging from Run 4, with a large proportion of starting units recovered in the final product. Such a procedure was used in Runs 9A and B and in Run 10 where the gains in specific activity were 35-, 30-, and 38-fold respectively. The recovery of units in the actual products were 32, 34, and 36·5 per cent. respectively (though taking into account samples removed for analysis and less active fractions not included in the product, some 54 to 66 per cent. of the total starting units could be accounted for). The yields of products were 80, 99·5, and 84 mg., which constituted 0·95, 1·15, and 0·95 per cent. of the original protein. These products also contained 7S γ globulin as revealed by immuno-electrophoresis and ultracentrifugal analysis (Figs 1 and 2, overleaf), but the bulk of the protein, *i.e.* 92 per cent. in Run 9A, 81 per cent. in Run 9B and 88 per cent. in Run 10, had a sedimentation coefficient of 19S or greater.

TABLE

COMPOSITION, ACTIVITIES, AND YIELDS OF RHEUMATOID FACTOR

Run No.	Case No.	Fractionation Procedure (for details of steps see following tables)			Ultracentrifugal (mg./		
		Step 1	Step 2	Step 3	27S	22S	19S
1	1	Euglobulin precipitation 1/I†	DEAE cellulose column chromatography		—	—	20
2 I	2	I Euglobulin precipitation 2/I	DEAE cellulose column chromatography		—	—	150
II		II Ammonium sulphate precipitation 2/II	DEAE cellulose column chromatography		—	—	70
3	3	Euglobulin precipitation 3/I	DEAE cellulose column chromatography	Zone centrifugation	—	—	63
4A	4	A Euglobulin precipitation A/Ia + Ib	Zone centrifugation		170	250	600
B		B Euglobulin precipitation B/I + II			70	450	830
5A	5	A Euglobulin precipitation 5/I	Zone centrifugation		—	30	210
B		B Euglobulin precipitation; Ammonium sulphate precipitation } 5/II + III	DEAE cellulose column chromatography { F.III		—	40	180
			F.IV		—	30	170
6	6	Zone centrifugation	DEAE cellulose column chromatography		—	—	330
7A	7	DEAE cellulose batch chromatography	Cohn low-temperature ethanol fractionation	DEAE cellulose batch chromatography	—	—	25
B		Cohn low-temperature ethanol fractionation	DEAE cellulose batch chromatography		—	—	33
8	8	DEAE cellulose batch chromatography	Cohn low-temperature ethanol fractionation	Zone centrifugation	—	—	104
9A†	9	} Euglobulin precipitation	Zone centrifugation { A		115	210	595
B			B		190	910	930
10A	10	Euglobulin precipitation	Zone centrifugation			15	795

* See p. 370. † Euglobulin precipitation. See Table III, *e.g.* 1/I for Run 1, Euglobulin precipitate I.

Euglobulin Precipitation

It has been the practice of various groups engaged in the study of rheumatoid factor to employ euglobulin precipitation as a first step (Svartz and Schlossmann, 1953; Kunkel and others, 1959; Lospalluto and Ziff, 1959). The crude precipitates thus obtained were found to contain most of the Rose-Waaler activity present in the original serum.

Euglobulin would therefore appear to be the most suitable starting material for the subsequent purification of rheumatoid factor. The composition of the euglobulin precipitated varied considerably, as did the efficiency of precipitating the rheumatoid factor without loss of activity (see Table III). These results suggest that there are uncontrolled factors involved in the precipitation of rheumatoid factor as water-insoluble euglobulin. One of these is undoubtedly the variability of the starting sera, all of which were obtained from different patients. In Serum 4B, almost all activity was precipitated after 24 hrs. while in Serum 5 very little had been precipitated after 48 hrs. Experiments recently performed show that, with Serum 5, the rheumatoid factor is efficiently recovered by diluting the serum 15-fold with cold de-ionized water. The most critical factor in these experiments, however, would appear to be the ionic strength to which the rheumatoid sera were finally adjusted.

Trial experiments performed on Sera 9 and 10 showed that, as with Serum 5, Rose-Waaler activity was most efficiently precipitated (80 and 62·5 per cent. of the total) with minimum contamination from other proteins, by diluting the serum 15-fold with cold de-ionized water at 4° C. and centrifuging

II

PREPARATIONS OBTAINED BY VARIOUS FRACTIONATION PROCEDURES

Product												
Composition (100 ml.)			Immunological Composition (mg./100 ml.)			Protein Concentration (mg./100 ml.)	Total Protein Recovery (mg.)	Per cent. Starting Protein	Total Units	Per cent. Units Recovered	Specific Activity	Specific Activity as per cent. of that of Original Serum
10S	7S	4·5S	α_2*	19Sγ*	7Sγ							
—	90	210	Not determined			320	6·4	0·3	320	15	50	2,900
—	25	470	Not determined			645	8·7	0·25	1,300	13	150	1,600
—	60	1,100				1,230	26·8	0·8	210	3	7·8	90
—	—	—	—	6	0·1	63	0·7	0·04	600	2	600	565
80	230	—	1	100	20	1,330	17·2	0·8	1,000	10	58	850
150	530	—	—	200	60	2,030	26·5	1·3	5,000	49	190	2,800
—	190	—	3	50	40	430	8·8	0·10	640	3	73	300
—	280	—	3	45	20	500	20·0	0·20	2,560	10	128	530
—	260	—	12	35	25	460	18·6	0·20	2,560	10	140	580
—	90	190	6	10	5	610	18·0	1·0	670	1·6	56	90
30	80	—	1	18	20	135	1·5	0·4	170	1·4	110	330
50	170	—	1	35	35	255	3·1	0·8	380	3	125	320
—	—	—	1	50	5	104	16·8	0·2	1,300	1·4	77	550
30	50	—	4	600	280	1,000	80·0	0·95	410,000	32	5,120	3,500
120	340		0	1,600	840	2,490	99·5	1·15	437,000	34	4,400	3,010
25	85		<3	700	240	920	84·0	0·95	117,000	36·5	1,390	3,820

down the precipitate almost immediately. Precipitates obtained by dialysis on the other hand of these sera against 14 volumes of de-ionized water and centrifuging down the precipitates at 2, 5, and 24 hrs, each time redialysing the supernatant, were very heterogenous as compared with the precipitates obtained by dilution, and the combined precipitate contained only 31 and 12·5 per cent. of the original activity. The greater heterogeneity of the "dialysis" products as compared with the "dilution" products was well shown by immuno-electrophoresis (see Fig. 2). The water-dilution technique was therefore adopted in Fractionations 9 and 10; the euglobulin precipitation, after suspension in the minimum volume of phosphate pH 6·9; M = 0·06 + 0·15 M NaCl, was found to contain 70 and 44·4 per cent. of the original units (Table III). Washing of precipitates was avoided, for, as shown in Run 4 and other unpublished work, quite an appreciable amount of activity may be removed by cold distilled water.

The variability between different euglobulin preparations noted above led to more detailed studies of euglobulin and rheumatoid factor precipitation with a series of tests on only two different sera (Table IV). (In order to measure the activities of the euglobulins, they were dissolved in a known volume of physiological saline, but varying amounts of precipitate remained insoluble as fine suspensions.) The highest recoveries of units were achieved by dialysing either of the water-diluted sera (2- or 4-fold) against 0·01 M phosphate buffer (pH 7·2), although almost as good yields were obtained by dialysis against distilled water. With the latter

TABLE

COMPARISON OF VARIOUS METHODS

Run Nos.	Fraction	Method of Preparing Euglobulin	Protein Precipitated (mg.)	Recovery	
				Per cent. Total Protein	Per cent. Total Units Precipitated
1	I	80 ml. serum against 2 litres for 48 hrs	99	3·2	40
	II III	Supernatant of I Supernatant of II	20	0·7	10
2	I	45 ml. serum (pH adjusted to pH 8 with 0·01 M phosphate buffer)	145	4·2	34
3	I	25 ml. serum Redialysed against 2 litres for 48 hrs	86	18·5	25
4A	I Ia	20 ml. serum diluted × 12 with tap water Distilled water washings of above	118	7·9	75
	Ib	Washed precipitate in 0·85 saline	63	4·7	25
	Ia + Ib	Ia + Ib redialysed	106	7·1	29
4B	I	Stepwise dialysis 20 ml. serum against tap water stirring	81	5·4	150
	II	Supernatant of I	25	1·7	3·8
	III	Supernatant of II	41	2·7	1·0
	IV	Supernatant of III	35	2·3	3·8
		Precipitates I + II in 0·85 saline redialysed	88	5·9	3·7
5	I	100 ml. serum against 5 litres tap water for 29 hrs stirring	325	2·9	3
	II	Supernatant I against running tap water for 20 hrs	130	1·2	5
9A		96 ml. serum + 1,400 ml. deionized water at 4° C. Centrifuged at 4,000 r.p.m. and 4° C. for 15 min.	482	5·75	70
10		100 ml. serum as above	450	5·1	44·4
2	II	Slow addition of saturated ammonium sulphate till solution 33 per cent. saturated	642	19·5	31
5	III		414	3·7	8·2

All dialyses performed against 1 litre glass-distille

* See p. 370.

method, however, there was generally more euglobulin precipitated and so the increases in specific activity were not as great. The efficiency of euglobulin precipitation was much greater with Serum B than with Serum A, as shown by the greater increase in specific activity. (Averaging the results of Experiments a, b, d, and e with each serum, the concentration achieved was three times greater with B than with A.) Dialysis against 0·05 M phosphate, physiological saline, and Ringer's solution invariably resulted in a considerable loss of units, confirming previous experiments. The specific activities of the euglobulins fell rapidly if the dialysis was continued for longer than 48 hrs.

Ion-exchange Chromatography

Analysis of the fractions obtained by DEAE cellulose chromatography of normal human serum (Stanworth, 1959) has indicated that 19S γ globulin can be readily separated from the major portion of the 7S γ globulin and from the 19S α_2 glycoprotein. This technique would therefore appear to be an ideal successive step to the initial euglobulin precipitation from rheumatoid serum, as it offers a means of freeing the rheumatoid factor from the co-precipitated 7S γ globulin. Such an approach in Fractionations 1, 2, 3, and 5B has provided the results given in Table V.

II

)F PRE..IPITATING EUGLOBULIN

Specific Activity as per cent. of that of Original Serum	Ultracentrifugal Composition (mg./100 ml.)						Immunological Composition (mg./100 ml.)		
	27S	22S	19S	10S	7S	4·5S	α_2*	19Sγ*	7Sγ
1,260	Not determined						Not determined		
1,600									
810	—	—	670	—	110	2,100	Not determined		
450	—	270	40	70	860	310	1	45	120
960	Not determined						Not determined		
910									
430	—	Trace	770	420	1,470	—	4	150	140
2,780	Not determined						Not determined		
225									
35									
160									
640	—	370	240	120	1,400	—	1	100	240
110		40	100	55	760	350	2	50	240
420		110	170	150	1,240	940	1	36	160
1,710	280	1,880	1,790	240	1,820	—	4	4,200	1,560
780		235	2,510	350 355 (12S)	1,550	—	3	2,000	1,600
210		—	640	—	540	10,500	Not determined		
210		50	220	260	3,840	760	200	200	2,560

ater for 24 hrs at 4° C. without stirring, except where stated.

Alternatively, DEAE cellulose chromatography would be useful in freeing rheumatoid factor from the bulk of 19S α_2 glycoprotein sedimented with it in zone-centrifugation procedures.

As will be observed from Table V, however, a disadvantage of the chromatographic procedure is the relatively poor yield of Rose-Waaler activity (always less than 50 per cent.) recovered from DEAE cellulose columns. This can probably be ascribed to the low recoveries of protein, particularly the macroglobulin. In this connexion, the batch chromatographic procedure (described later) was found to be more useful. As far as purification of rheumatoid factor is concerned, the column chromatographic procedure was found to increase the ratio of 19S to 7S γ globulin, as shown in the results of Fractionation 5 (Table V), although 7S γ globulin was not completely removed.

As would be expected from the analysis of normal serum chromatographic fractions, DEAE cellulose chromatography proved incapable of freeing euglobulin precipitates from contaminating 4·5S components (Table V).

Concentration of Chromatographic Fractions

In ascribing loss of activity to the column chromatographic treatment, it is important to consider the contribution made by the subsequent

TABLE IV

EFFICIENCY OF SEPARATION OF RHEUMATOID FACTOR BY

Material	Volume (ml.)	Method	Dilution	Supernatant 1 Volume (ml.)	1/Titre	1 × 2 Total Units of Activity Recovered	Per cent. of Units Recovered	3 Protein Concentration (mg./ml.)	1 × 3 Total Protein (mg.)
"A"	2	Neat serum	—	2	512	1,024	100	97	194
(a)	2	× 2 dilution dialyse H_2O	1/16	4	52	128	12·5	34	136
(b)	2	× 2 dilution dialyse 0·01M	1/16	4	32	128	12·5	40	160
(c)	2	× 2 dilution dialyse 0·05M	1/16	4	64	256	25	35	140
(d)	2	× 4 dilution dialyse H_2O	1/18	8	4	32	3·2	21	168
(e)	2	× 4 dilution dialyse 0·01M	1/18	8	32	256	25	26	208
(f)	2	× 4 dilution dialyse 0·05M	1/18	8	64	512	50	20	160
(g)	2	Dialyse against N. NaCl	1/15	2·4	256	614	60	69	165
(h)	2	Dialyse against Ringer's solution	1/15	2·3	256	588	57	72	163
"B"	2	Neat serum	—	2	512	1,024	100	87	174
(a)	2	× 2 dilution dialyse H_2O	1/16	4	64	256	25	39	156
(b)	2	× 2 dilution dialyse 0·01M	1/16	4	32	128	12·5	32	128
(c)	2	× 2 dilution dialyse 0·05M	1/16	4	256	1,024	100	32	128
(d)	2	× 4 dilution dialyse H_2O	1/18	8·5	32	272	27	19	162
(e)	2	× 4 dilution dialyse 0·01M	1/18	9	16	144	14	17	153
(f)	2	× 4 dilution dialyse 0·05M	1/18	8·5	256	2,180	213	23	195
(g)	2	Dialyse against N. NaCl	1/15	2·4	512	1,230	120	72	170
(h)	2	Dialyse against Ringer's solution	1/15	2·4	256	615	60	75	180

TABLE V

ACTIVITIES AND COMPOSITIONS OF RHEUMATOID FACTOR

Run	Sample	Protein Applied (mg.)	Protein Recovered (mg.)	Per cent. Protein Recovered	Units Applied	Total Units Recovered	Per cent. of Units Recovered
1	Euglobulin	78	39	50	1,720	330	19
2	Euglobulin I	115	46	40	8,800	1,230	14
	Euglobulin II	220	40	18	8,800	360	4
3	Euglobulin	81	—	—	38,000	I 2,200 II 15,360	46
5	Euglobulin II + III	395	239	60	24,350	8,100	33
6	Zone Centrifuge Fraction	47	—	—	17,900	1,022	6
7A	Serum	765	700	91	25,600	21,282	83
	Cohn Fraction I of Batched Serum	90	123	137	7,680	1,540	20
7B	Cohn Fraction I of Serum	35	38	109	15,360	3,580	23
8	Serum	6,900	6,700	97	97,000	51,100	53

Roman figures (*e.g.* I and II) denote different chromatographic fractions.

* See p. 370.

"Active Fraction" =

IV

VARIOUS METHODS OF EUGLOBULIN PRECIPITATION

	⅓ = S		4	Precipitate (in 2 ml. saline)						
						5			4/5	
Per cent. Protein Recovered	Specific Activity	Specific Activity as per cent. of that of Initial Serum	1/Titre	Total Units of Activity Recovered	Per cent. of Units Recovered	Protein Concentration (mg./100 ml.)	Total Protein (mg.)	Per cent. Protein Recovered	Specific Activity	Specific Activity as per cent. of that of Initial Serum
100	5·3	100								
70	0·9	17	128	256	25	4	8	4·1	32	600
83	0·8	16	64	128	12·5	2	4	2·0	32	600
72	1·8	34	8	16	1·5	1·2	2·4	1·2	6·6	120
87	0·2	4	128	256	25	2·8	5·6	2·9	48·5	920
108	1·2	23	128	256	25	2·6	5·2	2·7	49·1	930
83	3·3	60	8	16	1·5	1·6	3·2	1·6	5	94
85	3·7	70	4	8	0·8	—	—	—	—	—
84	3·6	68	4	8	0·8	2·0	4·0	2·0	2	38
100	5·9	100								
90	1·6	27	256	512	50	3·7	7·4	4·3	67·5	1,150
73	1·0	17	512	1,024	100	2·5	5·0	2·9	204	3,460
73	8·0	140	8	16	1·5	2·0	4·0	2·3	4	88
93	1·7	29	512	1,024	100	3·5	7·0	4·0	146	2,500
88	0·9	16	512	1,024	100	2·6	5·2	3·0	197	3,340
112	11·2	190	8	16	1·5	0·6	1·2	0·7	13·2	200
98	7·1	120	4	8	0·8	0·7	1·4	0·8	5·7	97
103	3·4	58	4	8	0·8	0·4	0·8	0·5	10	170

V

PREPARATIONS OBTAINED BY DEAE CELLULOSE CHROMATOGRAPHY

"Active" Fraction			Composition of "Active" Fraction (mg./100 ml.)							
			Ultracentrifugal					Immunological		
Units	Specific Activity	Specific Activity as percentage of that of Material Applied	22S	19S	10S	7S	4·5S	α_2*	19Sγ*	7Sγ
320	50	230	—	20	—	90	210	Not determined		
1,200	150	200	—	150	—	25	470	Not determined		
210	7·8	40	—	170	—	60	1,090			
2,200	116	20	80	130	70	210	350	6	100	30
15,360	2,110	430	—	210	—	—	550	Not determined		
III 2,560	128	210	40	180	—	280	—	3	45	20
IV 2,560	140	230	30	170	—	260	—	12	35	25
I, II 1,022	I 52, II 69	20	—	330	—	90	190	5	10	5
15,000	59	180	Not determined							
900 After concentration 170	110	60	—	250	30	80	—	1	18	40
2,400 After concentration 380	105	120	—	35	50	170	—	3	50	60
34,700	64	460	—	45	20	65	370	3	50	40

Chromatographic fraction containing majority of serological activity.

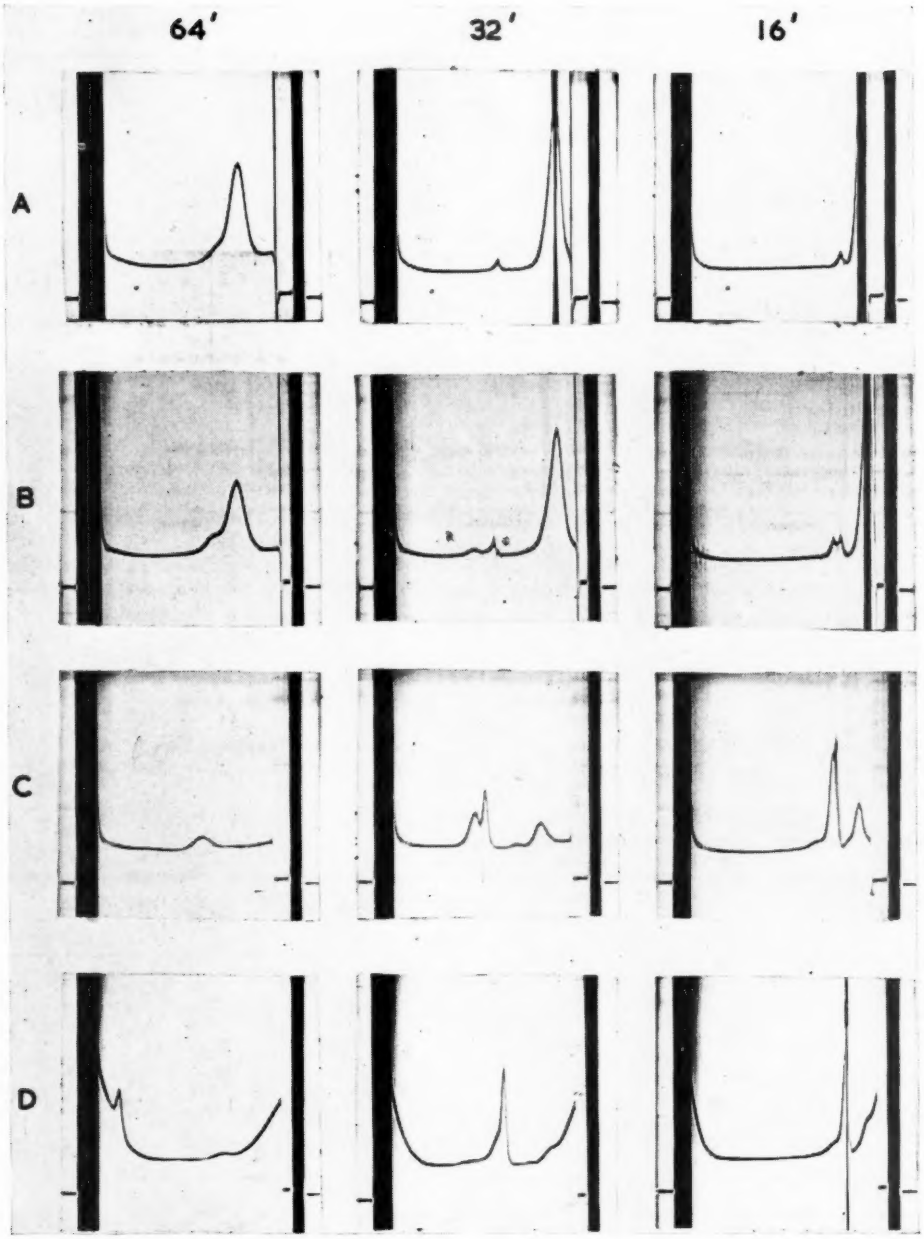

Fig. 1(A).—Normal serum (diluted 1 : 5).

Fig. 1(B).—Rheumatoid serum (No. 9, patient F.A., diluted 1 : 5).

Fig. 1(C).—Euglobin preparation from (B) above (diluted 1 : 5).

Fig. 1(D).—Zone centrifugation, high molecular weight fraction from above.

Solvent: phosphate buffer pH 6·9; M = 0·06 + 0·15M NaCl.

Speed: 60,000 r.p.m.; temperature 20° C.

Note presence of abnormally large amounts of 19S and 22S fractions in (B) and the progressive concentration and purification of the high molecular weight components in (C) and (D).

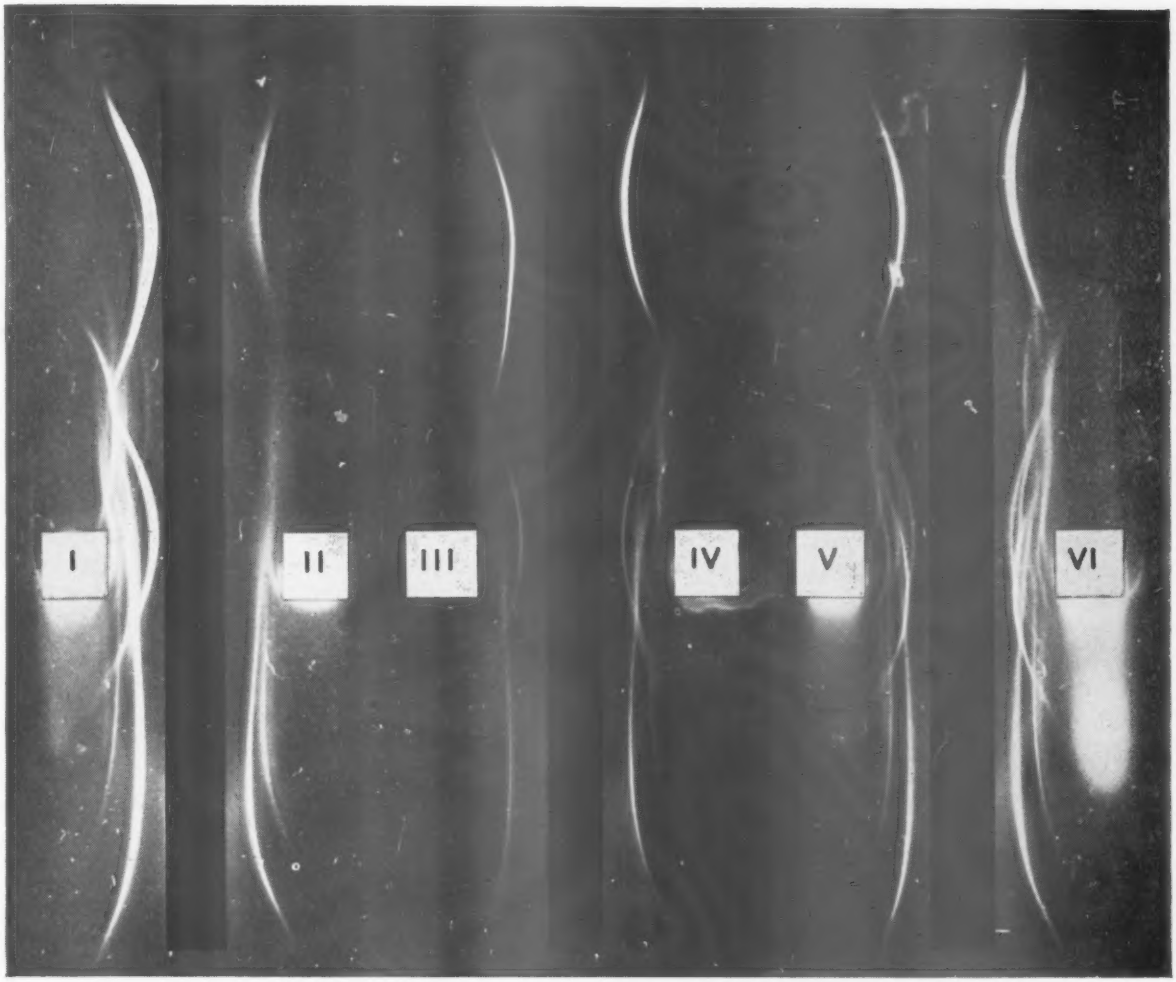

Fig. 2(I).—Rheumatoid serum (No. 9).

Fig. 2(II).—Euglobulin precipitate from (I) above prepared by dilution with de-ionized water (1 : 15).

Fig. 2(III).—Supernatant from (II).

Fig. 2(IV), (V), (VI).—Successive harvestings of euglobulin precipitates after dialysis of rheumatoid serum No. 9 against de-ionized water (15 volumes) with slow stirring for 2, 5, and 23 hrs respectively. Immuno-electrophoresis performed in 0·8 per cent. agar in barbitone buffer (pH 8·6; I=0·05). A current of 15 ma. was passed for 4 hrs.
Antiserum—anti normal human serum.

Note: In γ globulin zone, 7S γ globulin can be seen as a prolonged asymmetric line in all samples. 19S γ globulin appears shorter between this and the cup in all samples except (III).

Euglobulin precipitate obtained by dilution (Sample II) consists mainly of 7S and 19S γ globulins with only small amounts of albumin and α_2 globulin. Supernatant (Sample III) appears substantially free from 19S γ globulin, at least in the dilution tested.

In contrast, euglobulins prepared by dialysis (Samples IV, V, and VI) are immuno-electrophoretically complex, and 19S γ globulin occurs in all these precipitates.

concentration of the dilute chromatographic fraction solutions. Various concentrating procedures have been adopted, none of which has proved entirely satisfactory.

For instance, as is shown in Table VI (opposite), losses of activity as high as 95 per cent. were recorded during concentration by negative pressure ultrafiltration through Visking dialysis tubing and by the carbowax (polyethylene glycol) technique described by Kohn (1959), whilst losses of 80 per cent. occurred during ultrafiltration through collodion thimbles accompanied by simultaneous dialysis against buffered saline. Recoveries by ultrafiltration through Visking tubing were improved by massaging adherent protein off the walls of the tubing before pouring off the liquid.

These results, which are similar to those reported by Stanworth (1959) in a study of the effect of various concentration procedures on horse dandruff reagin, suggest that rheumatoid factor is highly susceptible to surface denaturation when purified.

An ultracentrifugal technique employed recently in the concentration of urinary colloid (Rowe and Soothill, 1961) would appear to offer improvements over the procedures just described, all of which involve the rheumatoid factor coming into contact with relatively large surface areas. A modification of this procedure, to avoid pellet formation in the bottom of the tube by using a bottom layer comprised of an inert non-water-miscible solvent (Stanworth and others, 1961), would appear to be advantageous.

In some instances, precipitation of rheumatoid factor from solution by dialysis against water proved a useful concentration procedure, but this was often vitiated by the disadvantage that the products were nearly always redissolved only with difficulty and accompanying denaturation. In order to overcome these difficulties in Runs 8 and 9, techniques were adopted which avoided the need for subsequent concentration.

Zone Centrifugation

Of all the fractionation procedures employed, zone centrifugation is undoubtedly the mildest as far as recovery of Rose-Waaler activity is concerned. This is indicated by the results given in Table VII, where it will be seen that 100 per cent. recoveries of activity are often achieved.

TABLE

ACTIVITIES AND COMPOSITIONS OF "RHEUMATOID FACTOR"

Run	Sample	Units Added	Specific Activity	Units Recovered	Specific Activity (Bottom of Tube)	Per cent. Units Recovered	Specific Activity as Percentage of that of Material Applied
1	Serum	64	1·7	112		175	
	Euglobulin I	128	22	128	28	100	130
	Euglobulin II	512	29	353	42·6	69	150
3	DEAE Chromatography Fraction†	2,880	116	2,700	Top 330 Bottom 120	94	280 100
	Top of above	1,920	330	680 or 1,280	600 or 1,200	35 or 70	180 or 360
4A	Euglobulin Ia + Ib	2,300	29	1,000	580	44	200
B	Euglobulin I + II	2,900	44	8,200	190	280	430
5‡	Euglobulin I	6,400	25	2,200	125	35	350
6‡	Serum	115,000	63	61,900	380	54	600
8‡	Cohn Fraction I of "Active" DEAE Batch Fraction	6,550	65	2,050	77	31	120
9A	Euglobulin	655,000	1,710	615,750	5,120	94	300
B		—	—	694,700	4,400	—	—
10	Euglobulin	126,000	780	176,000	3,820	140	490

* See p. 370.

† Mixing occurred on slicing tube—therefore top centrifuged again.

‡ Zone-centrifugation carried

Zone centrifugation was usually used as a final step in the removal of low molecular weight (7S) γ globulin contaminant from rheumatoid factor, the other 19S component (*i.e.* α_2 glycoprotein) having been previously removed by euglobulin precipitation and DEAE cellulose chromatography. Adoption of zone centrifugation as a preliminary step, as in Fractionation 6, did not prove very satisfactory; a drawback with these large starting volumes is the necessity of using angle rotors in order to be able to process sufficiently large volumes of rheumatoid serum. This has led to the contamination of the 19S zone with low molecular weight serum constituents (as shown in the results in Table VII).

DEAE Cellulose Batch Chromatography

With the aim of increasing the speed of the chromatographic procedure and improving yields, a batch process (Stanworth, 1960) was tried in the isolation of rheumatoid factor. As shown in Table V, protein recoveries of the order of 90 per cent. were obtained when rheumatoid serum was fractionated initially in this way (as in Fractionations 7A and 8). Corresponding improved recoveries (53 to 83 per cent.) of Rose-Waaler activity were also recorded, although this might reflect to some extent the superiority of whole serum as starting material in preference to euglobulin (used in the column procedures in Fractionations 1, 2, 3, 5, and 6). In considering recoveries of both protein and rheumatoid activity, one must bear in mind that in the batch procedure the final eluent was 1·5 M NaCl.

The batch chromatographic technique achieved similar resolution of serum proteins to that obtained by the column procedure, the eluate containing 19S γ globulin being contaminated with 4·5S component and also with relatively small amounts of 7S γ globulin. Further purification was accomplished on these occasions by a subsequent Cohn low-temperature ethanol fractionation procedure, as modified by Dr. K. W. Walton. Rose-Waaler activity was found to be completely precipitated along with the γ globulins, leaving behind in solution both 19S α_2 glycoprotein and 4·5S albumin contaminants.

The poor recovery of activity in Fractionation 8, where the modified Cohn technique was employed as a second step after DEAE cellulose batch chromatography, was probably due to denaturation of either the rheumatoid factor or of traces of 7S γ globulin, which may then inhibit the Rose-Waaler tests (Franklin, 1960), brought about by the addition of relatively large volumes of 0·1 M NaOH solution to adjust the pH to 7·4.

In Fractionation 7A, a repeat batch chromatographic procedure was made after Cohn fractionation, in an attempt to remove the remaining 7S γ globulin. Unfortunately, however, although overall 100 per cent. recovery of protein was achieved, only a 20 per cent. recovery of Rose-Waaler activity was recorded (Table V).

For this reason, zone centrifugation was adopted as the final step in Run 8, resulting in a 35 per cent. recovery of Rose-Waaler activity. This product contained only 19S protein as revealed by ultracentrifugal analysis (see Table II), but immunological analysis revealed 5 mg./100 ml. of 7S γ globulin and traces of α_2 glycoprotein.

Discussion

In this work on the isolation of rheumatoid factor, emphasis has been placed on the quantitative approach, often neglected in earlier studies. For instance, the enrichment of factor after each fractionation has been followed by measuring Rose-Waaler activity and relating this to total protein concentration. On this basis, results have been expressed in terms of "specific activity". Attempts have also been made to determine the yields of active material from the arithmetical products of the specific activities of solutions with their volumes. It is readily admitted that individual quantitative assessments are somewhat approximate because of the inaccuracies inherent in the use of limiting dilution values as indices of Rose-Waaler activity. No other methods of assaying rheumatoid factor activity have been employed.

The ability to precipitate rheumatoid factor as euglobulin varied considerably from serum to serum. This may reflect the properties of the sera or critical differences in the methods of precipitation.

In Table IV, showing experiments performed under identical conditions with the different sera, this variability is clearly seen. It would thus appear that one of the major factors controlling the precipitation of rheumatoid factor by dialysis or dilution lies in the starting serum. Prolonged dialysis of serum results in the precipitation of large amounts of "inactive protein" (Table III, Run 4B), with a considerable drop in specific activity. This drop in specific activity, usually accompanied by an overall loss of units, is probably due to some form of denaturation of rheumatoid factor; it might also, however, be due in part to the production of aggregated 7S γ globulin which is able to neutralize the rheumatoid factor by combining with it (Frank-

TABLE VI

COMPARISON OF THE EFFICIENCY OF VARIOUS METHODS OF CONCENTRATING CHROMATOGRAPHIC FRACTIONS CONTAINING RHEUMATOID FACTOR

Run	Fraction	Method of Concentration	Concentration Factor	Units Added	Units Recovered	Per cent. of Units Recovered	Per cent. Protein Recovered
1		Ultrafiltration through Visking tube (Grant, Rowe, and Stanworth, 1958)	25	570	320	56	Not determined
2	I	Ultrafiltration through Visking tube (Grant, Rowe, and Stanworth, 1958)	100	2,500	1,300	52	Not determined
3	II	Polyethylene glycol (Kohn, 1959)	3	7,600	380	5	50
5		Ultrafiltration through collodion thimbles with simultaneous dialysis	1	1,300	310	24	Not determined
6	I II	Ultrafiltration through collodion thimbles with simultaneous dialysis Ultrafiltration through Visking tube with simultaneous dialysis	14	20,000	1,000	5	Not determined
7A B		As Run 5	7 7	2,400 900	380 170	16 19	Not determined

Note: Above fractions are final products.

VII

PREPARATIONS OBTAINED BY ZONE CENTRIFUGATION

Ultracentrifugal Composition (mg./100 ml.)												Immunological Composition (mg./100 ml.)					
Initial						Final						Initial			Final		
27S	22S	19S	10S	7S	4·5S	27S	22S	19S	10S	7S	4·5S	α_2*	19SY*	7SY	α_2*	19SY*	7SY
	—	130	—	840	2,730	Not determined						Not determined					
Not determined																	
	130	170	100	280	420	Not determined						6	100	3	Not determined		
Not determined						—	—	63	—	—	—	Not determined			—	6	0·1
	Trace	770	420	1,470	—	170	250	600	80	230	—	4	150	140	1	100	20
	370	240	120	1,400	—	70	450	830	150	530	—	1	100	240	—	200	60
	40	100	55	760	350	—	30	210	—	190	—	3	50	240	3	50	40
	—	100	—	1,000	7,000	−9	—	270	—	780	1,010	75	65	1,280	5	10	5
	16	160	130	190	—	—	—	104	—	—	—	1	200	20	1	50	5
280	1,880	1,790	240	1,820	—	115	210	595	30	50	—	4	4,200	1,560	4	600	280
						190	910	930	120	340	—				0	1,600	840
	235	2,510	355 350 (12S)	1,550	—		15	795	25	85	—	<3	2,000	1,600	<3	700	240

out in 40 angle head rotor at 36,000 r.p.m.

lin, 1960), and to the precipitation of protein such as albumin which does not agglutinate sensitized sheep cells. Experience with Sera 5 and 9 would indicate that, with some sera at least, a water-dilution technique is more efficient than dialysis against water. Dilution will certainly have a more profound effect on interionic and intramolecular forces which in sera may tend to solubilize the rheumatoid factor. This technique also prevents the ionic strength from falling to zero level as obtained in complete dialysis and hence reduces the probability of denaturation.

Of the further procedures available for increasing the specific activity of rheumatoid factor preparations, chromatography on DEAE cellulose and zone ultracentrifugation have been most extensively employed. The efficiencies of such procedures may be classified in terms of yield of desired product, concentration of product without further manipulation, and discrimination between individual proteins. Rheumatoid euglobulin prepared by dilution or dialysis was desirable as starting material for zone ultracentrifugation, for it contained little 19S high molecular weight glycoprotein which would sediment with the rheumatoid factor.

In terms of discrimination, zone centrifugation can only be expected to separate proteins of the 19S class and greater molecular weight from other serum proteins, and even this achievement requires special arrangements, such as suitable density gradients and minimum disturbance during the sampling of the tubes. In these experiments zone centrifugation did not achieve complete separation of 19S protein from 7S and 10S material, but the majority of these proteins were removed. Re-centrifugation could have been adopted, but was avoided partly because repeated ultracentrifugation of rheumatoid factor had been shown to decrease its activity (Svartz and others, 1958) and also involved redialysis of the sample.

Column chromatography on DEAE cellulose enables the separation of rheumatoid factor from the bulk of the 7S γ globulin precipitated as euglobulin, but complete separation was not achieved. Losses of protein and activity were always considerable. Products obtained by chromatographic techniques were usually contaminated with 7S γ globulin, albumin if this was present in the euglobulin, traces of α_2 high molecular weight glycoprotein, and β lipoprotein, and contained large amounts of 19S γ globulin. It is thus essential that this step be followed by zone ultracentrifugation to remove low molecular weight contaminants.

Batch chromatography achieved a separation similar to that obtained by the column technique, but total recovery of both protein and units was usually much better. The superiority of the batch chromatographic procedure over the column procedure, in addition to that of speed, may depend on the rheumatoid factor (and other proteins) being attached to the resin for a minimum period of time and so being less likely to be irreversibly denatured.

The lower losses of activity associated with the zone ultracentrifugation procedure could be attributed to the "milder" conditions experienced in this method, which avoids precipitation and adsorption on to resins with subsequent solubilization and elution—procedures which may produce denaturing of the molecule. The use of a sucrose density gradient may help to protect the rheumatoid molecule.

One possible index of denaturing available for the results of these studies lies in the appearance of additional ultracentrifugal components, *e.g.* 27S, 22S, and 10S. Four of the starting sera contained 22S material, and three also contained 10S protein. Whether or not these proteins were originally present in the sera or were produced on storage at $-20°$ C. is not known, but Svartz (1960) believes that the rheumatoid factor is pre-existent in the blood as a globulin with a sedimentation coefficient of 18 to 19S.

The 10S component detected, particularly on euglobulin precipitation and Cohn fractionation, would appear to be produced during the experimental procedure. There is no evidence to suggest that this material resulted from the action of soluble γ globulin aggregates in a manner analogous to the effect of adding soluble γ globulin aggregates to normal human sera followed by incubation at 4° C. (as described by Muller-Eberhard and Kunkel, 1960).

As purification proceeds, the rheumatoid factor becomes more susceptible to denaturing and therefore it is perhaps not justifiable to compare different fractionation procedures unless they were performed on the same starting material. Susceptibility to denaturing could be due to the removal of protective compounds, such as 7S γ globulin which forms 22S derivatives with 19S γ globulin. Experiments performed by dialysing rheumatoid sera against 0·85 per cent. buffered saline and Ringer's solution, with little or no precipitation of euglobulin, results in the loss of a considerable amount of serological activity, suggesting the removal of dialysable activators which could include metal ions or compounds such as cysteine and ascorbic acid which may influence the surface groups of the molecule (*e.g.* sulphydryl groups). Decrease in activity

could also be attributed to denaturing of the molecule itself or inhibition by aggregated 7S γ globulin, but under the above conditions we should expect both of these effects to be at a minimum.

The special efforts that have been made to measure the amounts of individual proteins present in the solutions by immunological methods have served two purposes. In the first place, it has been useful as a guide to the specific discriminatory powers of special procedures, in particular, euglobulin precipitation. It was also hoped by means of this approach to obtain further information about the nature of the rheumatoid factor, in particular its relationship to 19S γ globulin. In this context it is interesting to note that, while the estimation of 7S component by analytical ultracentrifugation and 7S γ globulin immunologically agreed reasonably well in most of the native sera, comparable analyses of preparations tended to show a considerable discrepancy explicable possibly in terms of the relative concentration of 7S components other than γ globulin. Other possible explanations include the interaction of 19S protein rheumatoid factor with 7S γ globulin thus impeding diffusion of this protein through the agar plate.

Work performed to date has not shown whether or not rheumatoid factor is distinct from 19S γ iso-agglutinins, or is a slightly altered 19S γ globulin. Increases in serological activity have shown no evident parallel with 19S γ concentrations as estimated immunologically. Attempts are now being made to see whether or not it is possible to resolve sheep cell agglutinating activity from iso-agglutinin activity.

Iso-agglutinin preparations from normal sera fail to give positive sheep cell agglutinating activity, although adsorbed by the sensitized sheep cell.

Summary

A detailed analysis has been made of methods previously used in attempts to isolate rheumatoid factor, including euglobulin precipitation, DEAE cellulose chromatography, zone centrifugation, and Cohn type low-temperature ethanol fractionation procedures.

The recovery of serological activity and increases in specific activity have been determined. The degree of resolution of the different techniques has been investigated by ultracentrifugal and immunological methods.

The most efficient way of preparing rheumatoid factor in a fairly pure state appears to be euglobulin precipitation by water dilution followed by zone centrifugation.

Methods involving euglobulin precipitation by prolonged dialysis against water or the addition of saturated ammonium sulphate, DEAE cellulose chromatography, and concentration procedures, such as ultrafiltration and carbowax (polyethylene glycol) techniques, were found to result in a considerable loss of serological activity.

With the techniques used to date it has not been possible to resolve rheumatoid factor and 19S γ globulin.

The authors wish to thank Professor J. R. Squire for his advice and encouragement. Dr. J. F. Soothill kindly performed the quantitative precipitin estimations. We are also indebted to Dr. K. W. Walton for help with his modified Cohn fractionation procedure, to Miss P. Ratcliff, who carried out the ultracentrifugal analyses (in a machine generously donated by the Rockefeller Foundation of New York), and to Miss A. Hudson, who performed the Rose-Waaler titrations. Rheumatoid sera were kindly provided by Dr. C. F. Hawkins of the General Hospital, Birmingham.

Finally, we wish to acknowledge the generous financial assistance provided by the Empire Rheumatism Council.

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Etudes sur l'isolement du facteur rhumatismal

RÉSUMÉ

On analysa minutieusement les méthodes employées jusqu'à présent dans les tentatives d'isoler le facteur rhumatismal, telles que le fractionnement par précipitation de l'euglobuline, la chromatographie sur la cellulose DEAE (diéthylaminoéthyl), la centrifugation zonale et le fractionnement à l'éthanol en température basse d'après Cohn.

On détermina la récupération de l'activité sérologique et l'augmentation de l'activité spécifique. Le degré de resolution obtenue par de différents procédés fut étudié par des méthodes immunologiques et ultracentrifuges.

La manière la plus efficace pour préparer le facteur rhumatismal en un état assez pur semble être la précipitation de l'euglobuline par dilution aqueuse, suivie de centrifugation zonale.

Des méthodes impliquant la précipitation de l'euglobuine par une dialyse prolongée à l'eau ou par l'addition de sulfate d'ammonium concentré, la chromatographie sur la cellulose DEAE, et des procédés de concentration, telles que l'ultrafiltration et des procédés au glycol de polyéthylène, aboutirent à une perte considérable d'activité sérologique.

Avec des procédés employés jusqu'à présent il ne fut pas possible d'isoler la facteur rhumatismal et la globuline gamma 19S.

Estudios sobre el aislamiento del factor reumatoide

SUMARIO

Se analizaron detalladamente los métodos empleados hasta ahora en las tentativas de aislar el factor reumatoide, tales como los procedimientos de fraccionamiento por precipitación de la euglobulina, cromatografía sobre celulosa DEAE (dietilaminoetil), centrifugación zonal y fraccionamiento por etanol en temperatura baja según Cohn.

Se determinó la recuperación de la actividad serológica y el aumento de la actividad específica. El grado de resolución por diversos procedimientos fué estudiado por métodos centrífugos e inmunológicos.

La más eficaz manera de preparar el factor reumatoide en un estado bastante puro parece ser la precipitación de euglobulina por dilución acuosa, seguida de centrifugación zonal.

Métodos que implican la precipitación de la euglobina por dialisis prolongada con agua or por añadidura de sulfato de amonio concentrado, la cromatografía sobre celulosa DEAE y procedimientos de concentración, tales como la ultrafiltración o el empleo de glicol de polietileno, ocasionaron una pérdida considerable de la actividad serológica.

Con los procedimientos empleados hasta la hora presente no fué posible resolver el factor reumatoide y la globulina gamma 19S.

Ann. rheum. Dis. (1961), **20**, 386.

A COMPARATIVE STUDY OF JOINT PAIN IN ADULT AND JUVENILE RHEUMATOID ARTHRITIS

BY

A.-L. LAAKSONEN AND V. LAINE

From the Rheumatism Foundation Hospital, Heinola, Finland (Chief: V. Laine, M.D.)

An observation by one of us that joints affected by rheumatoid arthritis are not as painful in children as in adults had led us to carry out a pilot study in order to investigate this finding. We have found no such statements in the literature.

Material and Methods

24 children aged between 4 and 14 years and suffering from rheumatoid arthritis were included in this study. Eight of them were 7 years old or less. As controls we used thirty patients with rheumatoid arthritis between the ages of 18 and 51, of whom eight were over 40 and only one was under 20 years old. In each group 95 affected joints (190 altogether) were carefully analysed regarding pain. Only the wrists, elbows, knees, and ankles were taken into account (Table I).

TABLE I
AFFECTED JOINTS

Patients	Juvenile	Adult	Total
Wrists	32	32	64
Elbows	18	18	36
Knees	27	27	54
Ankles	18	18	36
Total	95	95	190
No. of Joints with Active Inflammation	33	33	66

The symptoms studied included hydrops, swelling, active inflammation, range of movement, pain on movement in extreme positions of the joint, pain on palpation, and pain on using the joint and on weight bearing. Only definite swellings were included in the series. A definite hydrops or increased circumference was estimated by comparison with the contralateral joint.

The skin temperature was used as a criterion of active inflammation. This was measured in standardized surroundings, and only joints showing a definite increase in skin temperature in comparison with the surrounding areas of the body or the contralateral joint were included.

The range of motion in each joint was determined several times in evaluating the pain on movement.

The degree of pain was estimated as follows:

$-$ = no pain,
$+$ = uncertain or slight pain,
$++$ = definite pain,
$+++$ = very severe pain.

The adult patients were selected so that the duration of the rheumatoid process in each case was approximately the same as in the children. In each group seven patients were receiving steroid treatment.

Results

Table II includes all the joints studied. There are more painless joints among the children, by each method of assessment. More adults experienced uncertain, slight, and moderate pain, but there was no great difference in the patients with very painful joints.

When only joints with active inflammation were taken into account (Table III, opposite), there was no difference between children and adults in pain due to passive movements in extreme positions of the joint. This was to be expected in cases with active inflammation, and it was therefore surprising that the results of other evaluations of pain showed a difference. The palpation and use of the joints does not cause the same tension in the inflamed structures,

TABLE II
PAIN IN ARTHRITIC JOINTS IN CHILDREN AND ADULTS

Source of Pain		Movement in Extreme Positions		Palpation		Use of Joint and Weight Bearing	
Patients		Children	Adults	Children	Adults	Children	Adults
Grading of Pain	$-$	45	29	83	47	74	42
	$+$	28	36	9	40	13	36
	$++$	18	28	3	7	6	15
	$+++$	4	2	—	1	2	2
Totals		95	95	95	95	95	95

TABLE III
PAIN IN JOINTS WITH ACTIVE INFLAMMATION IN CHILDREN AND ADULTS

Source of Pain		Movement in Extreme Positions		Palpation		Use of Joint and Weight Bearing	
Patients		Children	Adults	Children	Adults	Children	Adults
Grading of Pain	—	9	8	29	13	22	8
	+	13	10	4	15	4	17
	++	8	14	—	5	5	6
	+++	3	1	—	—	2	2
Totals		33	33	33	33	33	33

and there is more scope for an individual to imagine or have a presentiment of pain. The children appeared to suffer less than adults when a painful joint was "loaded".

The exclusion of cases under treatment with corticosteroids did not change the results.

There are differences in the pain experienced in various joints. In those with a small joint cavity and a complex of anatomy intense pain is experienced in movement in extreme positions. The wrists, ankles, and elbows are joints of this kind, and in them there was no difference between children and adults. A clear-cut difference was found on palpation and on "loading" the joint. In the elbow, however, the loading mechanism was not used correctly, and the results are thus indecisive.

The number of patients was too small to determine whether the children's ages had any effect on the amount of pain experienced.

Discussion

The results tend to support the observation that children suffering from rheumatoid arthritis suffer less discomfort in the affected joints than adults.

If the concept of the two mechanisms involved in the phenomenon of pain is accepted as a hypothesis, these results can be easily explained. The physical phenomenon of pain, mediated through nervous connexions, is developed during pre-natal life and is ready to serve at the very first moment of life. The psychical component develops later during life and is by no means constant, being a very complex, changeable manifestation of mental life (Hardy, Wolff, and Goodell, 1952). The reactions of children to pain may thus differ from that of adults, because of the different stage of mental development.

If this concept is accepted, the significance of pain in rheumatoid arthritis can be better understood and evaluated, and this may influence the treatment of pain and evaluation of disability in rheumatoid arthritis.

Summary

A comparative study has been made of the pain experienced in the affected joints of juvenile and adult patients suffering from rheumatoid arthritis. 95 corresponding joints in each group of patients were studied, as regards pain on movement of the joint in extreme positions, pain on palpation, and pain on using the joint and weight bearing.

The results tend to confirm the observation that children suffer less discomfort from joints affected by rheumatoid arthritis than adults, because children react differently to pain.

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Etude comparée de la douleur articulaire dans l'arthrite rhumatismale adulte et juvénile

RÉSUMÉ

On procéda à une étude comparée de la douleur ressentie dans les articulations affectées par des malades jeunes et adultes atteints d'arthrite rhumatismale. On étudia 95 articulations correspondantes dans chaque groupe de malades en ce qui concerne la douleur au mouvement de l'articulation en positions extrêmes, à la palpation, au mouvement actif et en état de supporter un poids.

Les résultats tendent à confirmer l'observation que les enfants sont moins incommodés par les articulations affectées que les adultes, parce que les enfants réagissent différemment à la douleur.

Estudio comparativo del dolor articular en la artritis reumatoide adulta y juvenil

SUMARIO

Se hizo un estudio comparativo del dolor sentido en las articulaciones afectas por enfermos jóvenes y adultos con artritis reumatoide. Se estudiaron 95 articulaciones correspondientes en cada grupo de enfermos respecto al dolor al mover la articulación en posiciones extremas, a la palpación, al movimiento activo y al soportar un peso.

Los resultados tienden a confirmar la observación que los niños padecen menos molestia en las articulaciones afectas por artritis reumatoide que los adultos, porque los niños reaccionan diferentemente al dolor.

Ann. Rheum. Dis. (1961), **20**, 388.

BOOK REVIEWS

Les osteo-arthropathies nerveuses (Neurological Osteo-Arthropathies). By A. M. Recordier, P. Mouren, and G. Serratrice, with an introduction by L. van Bogaert. 1961. Pp. 167, 50 figs, bibls. Expansion Scientifique Française, Paris.

There are not many works on the joint lesions complicating neurological disorders and a new book is to be welcomed. The diseases covered include tabes, syringomyelia, leprosy, diabetic neuropathy, Thevenard's disease (a rare familial mutilating acropathy), para-osteo-arthropathy (ossifications of soft tissues near paralysed joints), and congenital indifference to pain. These are all diseases in which there is an absent or diminished pain sensibility for the protection of the joint. In addition, the authors include sections on the painful inflammatory and wasting dystrophies, such as the shoulder-hand syndrome, Sudeck's atrophy, and the postherpetic osteoporosis which may follow a neurological disease. It is useful to have these subjects brought together; the authors have read widely and have gone to great trouble to assemble their material in an orderly and readable fashion. Indeed, one cannot help wondering if they are not too involved in niceties of classification in a subject in which our knowledge of the disordered physiology is still scanty, and experimental observations are few. Each section starts with a brief recital of the names of the numerous authors who have written on the subject, and ends with an extensive bibliography, mainly devoted to papers from continental authors. It is provoking for the English-speaking reader to find that the reference system is often impossible to follow. With some chapters, such as that on tabes, there is a reasonable hope that an authority referred to in the text will be found in the list of references, but in the opening chapter devoted to a justification of concept of a neurological osteo-arthropathy, there are 44 references in the text, only five of which appear amongst the 71 in the reference list. In discussing lesions of the medulla followed by reflex dystrophies involving the limbs, the authors twice refer to the experiments of d'Albertoni (who is said to have produced haemarthroses in animals by trauma to the medulla), yet they fail to give a reference to this author in the bibliography, so that the reader cannot take this interesting observation further without extensive research. The illustrations all consist of reproductions of radiographs, of moderate quality. No clinical photographs are shown, and only two actual case histories enliven the formal clinical descriptions of the various maladies. The book is interesting to read, because it is about an interesting subject, and the review of Thevenard's disease and its variants is very good, but those seeking information about the other diseases, unless they are particularly interested in the continental literature, would do better elsewhere.

A. St. J. Dixon.

VIII Scandinavian Congress of Rheumatology.

The proceedings of the eighth Scandinavian Congress of Rheumatology, held in Finland during June, 1960, are published in Nos. 1 and 2 of Volume 7, 1961, of the *Acta Rheumatologica Scandinavica*. The two issues contain 31 papers. From the summaries of many of these papers, the following brief observations are made, the names of the authors being shown in brackets.

A haemagglutinating substance with properties similar to the "rheumatoid factor" has been produced experimentally in white rats and pigs by injections of a diplostreptococcus isolated from rheumatoid subjects (Svartz). The "specific" haemagglutinating substances of the Gm system and the substances responsible for the Waaler-Rose test are probably closely related but separate macroglobulins (Harboe). Even refined techniques for the titrations of complement and the complement components fail to yield data to sustain an autoimmunological pathogenesis for rheumatoid arthritis and spondylitis ankylopoietica (Jonsen and Kåss). The micro-analysis of the trabecular structure of cancellous bone gives a fair idea of the mineralization grade of the bone tissue, provided that the trabecular pattern is not irregular as it is in rheumatoid arthritis (Virtama). In the study of electrocardiographic changes, the increased 1-noradrenalin secretion might constitute an additional link to the pathogenesis of rheumatic fever (Järvinen). Trauma and infection appear to be important elements in the aetiology of osteo-arthrosis (E. Jarløv, Brinch, and N. V. Jarløv). In the appraisal of rheumatoid deformities of the hand and their treatment, the function is often adequate despite the deformities; discussion of the place of surgical procedures (Pulkki).

The need for orthopaedic surgery was found to increase with duration of rheumatoid arthritis; 1,227 operations were performed in 758 patients in an unselected series of 4,527 patients in Heinola (Vainio and Hurri). Carrageenin granulomata showed an increase in uptake of radioactive proline into collagen fractions when incubated with beta-aminopropionitrile (Kulonen). A follow-up of 829 rheumatic cases in Västerës, Sweden, emphasizes the great importance of special rehabilitation units and a scheme for this purpose is discussed (Bjure). Prognostic value is attached to the titre of the Waaler-Rose test, which is more closely related to deep-seated anatomical alterations than the fluctuating state of inflammation (Tönder and Quamme). Reiter's syndrome complicated by universal keratosis blennorrhagica (Oka and Hiltunen). Adenosine triphosphatase activity in erythrocytes of rheumatoid arthritis did not differ from that of healthy controls (Györki and Sandell). 30 per cent. of 203 rheumatoid arthritics had reduced kidney function, which is a part of the disease itself (Sørenson).

Harry Coke.

Drugs in the Treatment of Disease. 1961. Pp. 570. B.M.A. Publications. (35*s*.)

This well-produced volume offers practical guidance on the use of drugs, both ancient and modern, in the various fields of medical practice. Each article was originally commissioned for publication in the *British Medical Journal*.

The two articles referring to rheumatology are by Dr. F. Dudley Hart: "Corticosteroids in Rheumatic Diseases" and "Analgesics in Rheumatic Diseases". In the former he discusses briefly but comprehensively the whole field. As he says: "The indications and contra-indications in these different disorders are in some measure a matter of individual opinion, but certain facts have been learnt in the hard school of experience." He adds the important rider: "In general it may be said that it is far easier to start steroid therapy than to stop it."

Both articles are full of practical good sense, which should appeal to the "expert" equally with the tyro.

A volume of this sort, which enables the busy practitioner to obtain authoritative practical information succinctly expressed, in the various fields of modern drug therapy, obviously fulfils a very useful purpose, as Dr. Hugh Clegg points out in his preface.

W. S. C. COPEMAN.

IV BRAZILIAN CONGRESS OF RHEUMATOLOGY

Pôrto Alegre, 1962

The IV Brazilian Congress of Rheumatology, sponsored by the Brazilian Society of Rheumatology and the Rheumatological Society of Rio Grande do Sul, will take place on May 15 to 19, 1962.

Particulars may be obtained from:

Sociedade de Reumatologia do Rio Grande do Sul,
Praça Júlio de Castilhos, 20,
Pôrto Alegre, Brazil.

GAIRDNER AWARDS 1961

Amongst the awards for the year 1961 by the Gairdner Foundation, which were announced in Toronto recently, is one to Dr. Jonas H. Kellgren, Professor of Rheumatology and Director of the Rheumatism Research Centre, University of Manchester, for his advanced studies of the incidence of rheumatoid arthritis. He has also made significant contributions to the better understanding of rheumatoid arthritis as a generalized connective tissue disease, and his work has led to improvements in diagnosis and treatment.

W.H.O. FELLOWSHIP 1961

Dr. B. S. Rose, medical superintendent, Queen Elizabeth Hospital, Rotorua, New Zealand, and formerly senior registrar and tutor in the department of child health and paediatrics, University of Leeds, has been awarded a W.H.O. Fellowship to study developments in rheumatology overseas.

OBITUARY

GUIDO COSTA BERTANI, 1899–1961

Argentinian rheumatology has suffered a further loss in the person of Dr. Guido Bertani, who died in July at the age of 62.

A severe attack of rheumatism in early life initiated his lifelong interest and pioneer work in this subject. He founded, and edited for 26 years, the *Revista Argentina de Reumatologia*.

He was a man of philosophical outlook and wide interests, and was at one time and another president of a number of learned Societies. W.S.C.C.

Ann. rheum. Dis. (1961), **20**, 390.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Joint Dislocation as a Sequel of Rheumatic Fever. (Le rhumatisme disloquant, séquelle articulaire de la maladie de Bouillaud.) RAVAULT, P. P., MAÎTREPIERRE, J., LEJEUNE, E., NORMAND, J., and CRETIN-MAITENAZ, R. (1961). *J. Méd. Lyon*, **42**, 101. 8 figs, 29 refs.

Since the original description of dislocation of joints as a sequel of rheumatic fever by Lereboullet and Mouzon (*Bull. Soc. méd. Hôp. Paris*, 1920, **44**, 86), the number of published cases has reached seventeen, to which the present authors contributed three (*Rev. lyon. Méd.*, 1956, **5**, 18 and 849). They now report six further cases occurring in patients aged between 14 and 39 (mean 25) years, in whom the dislocations appeared 4 to 25 years after the first attack of rheumatic fever, during which time the patients had suffered a number of relapses. In twenty of the 23 published cases, cardiac lesions were also present. The authors state that the dislocations take up to 3 months to develop, are easily reducible, show no tendency to progress, and cause little inconvenience; they appear to be due to excessive laxity of the joint capsules and ligaments. The joints most commonly affected are the metacarpo- and metatarso-phalangeal; ulnar deviation of the hands and hallux valgus with hammer-toe of the adjoining toe are also often seen. Prophylactic treatment at an early stage by suitable splinting is advocated. *D. Preiskel.*

Group-A Beta-Haemolytic Streptococci and Rheumatic Fever in Miami, Florida. IV. Correlation between School Absenteeism, the Isolation of Beta-Haemolytic Streptococci, and Antistreptolysin-O Serum Responses. SASLAW, M. S., and STREITFELD, M. M. (1961). *Dis. Chest*, **39**, 92. 11 refs.

The authors of this paper, from the National Children's Cardiac Hospital, Miami, and the University of Miami, report the results obtained by swabbing the throats of 333 school children at monthly intervals during the 8-month period October, 1954, to May, 1955. A total of 533 isolations of Group-A β-haemolytic streptococci (Gp-A H.S.) were made. The isolations were grouped according to the number of colonies on the plate and analysed according to whether the child was at school at the time or absent from school for medical reasons. Similar analyses were made for the isolations of streptococci of various other groups. Gp-A H.S. were found in 38 (58·5 per cent.) of 65 children absent with upper respiratory infections as against 72 (37·1 per cent.) of 194 children not absent at the time of swabbing. When an "epidemic" of Gp-A H.S. (Type 6) occurred, there was no increase in the number of absences due to upper respiratory illness. No marked correlation could be established between absenteeism and isolation of Gp-A H.S., the occurrence of a two-tube rise in serum anti-streptolysin-O level, the number of colonies of Gp-A H.S. grown from the throat swabs, or the isolation of streptococci of other groups. The low rate of absence due to respiratory infection, combined with the fact that Gp-A H.S. isolations could be associated with an immunological reaction yet not cause absence from school for medical reasons, suggested that the authors were dealing with relatively resistant hosts or relatively avirulent organisms. No cases of acute nephritis or rheumatic fever occurred among the children during the period of study. *Allan St. J. Dixon.*

Limited Clinical Evaluation of an Egg-Yolk Fraction in the Prevention of Rheumatic Recurrences. COBURN, A. F., and RICH, H. (1960). *A.I.R.* (*Rio de J.*), 3, 498. 24 refs.

There is circumstantial evidence that improved diet, particularly an increase in the number of eggs consumed, lowers the incidence of attacks of rheumatic fever, and in animal experiments N-(2-hydroxyethyl)-palmitamide (HEP), a fraction of egg yolk, has been shown to have anti-allergic properties in guinea-pigs. The study reported in this paper from New York Medical College was undertaken to determine if HEP could protect susceptible children against recurrent attacks of rheumatic fever and was carried out on 95 children from indigent New York families who had previously been in-patients for rheumatic fever, 152 siblings serving as controls. No antibacterial chemoprophylaxis was given to the patients. It had been previously estimated (from the known recurrence rate of rheumatic fever) that this number of subjects would be sufficient to detect a protective effect of HEP.

A placebo-controlled double-blind study was set up and arrangements made for periodic supervision, throat swabbing, and estimation of antistreptolysin-O titres.

In the event, no firm conclusions could be drawn from the study because the expected number of recurrences among the controls did not occur. The authors cite evidence for a considerable improvement in the diet of their subjects (including an increased consumption of eggs) during the period of observation, which may have interfered with the conditions of the study as originally planned. Despite the fact that nearly all subjects developed Group-A streptococcal infections at some time, only seven recurrences of rheumatic fever were seen, and only one (which occurred a few weeks after starting treatment) was in the HEP-treated group. Although the results of this investigation failed to reach significance at the 5 per cent. level, they are nevertheless regarded as promising. *Allan St. J. Dixon.*

Serological Investigations into Sequelae of Scarlet Fever with Particular Reference to Rheumatic Fever. POPOV, N. (1961). *Arch. Dis. Childh.*, **36**, 77. 2 figs, 13 refs.

The study herein reported is based on the results of detailed clinical and serological studies in 31 children treated at the Second City Children's Hospital, Sofia, Bulgaria, for scarlet fever and followed up for more than 2 years. The serological factors studied included the response to the C-reactive protein test, the erythrocyte sedimentation rate, the plasma fibrinogen level, and the titres of antistreptolysin-O (ASO) and heterophil agglutinins. Evidence of autoimmunization was sought for in the response to the Coomb's test and the antihuman globulin consumption test of Steffen and in the Rose-Waaler reaction.

Although there was a remarkably high incidence of complications, such as recurrent sore throat and otitis media in 21 of the children, rheumatic fever did not develop in any of the patients. There was no instance of dysproteinaemia, of hyperfibrinogenaenia, or of an extremely high ASO titre, changes which the author accepts as characteristic of rheumatic fever. He therefore concluded that there "was no ground for considering that the post-scarlet fever period was immunobiologically identical with the acute phase of rheumatic fever".

L. E. Glynn.

Bed Rest, Salicylates, and Steroids in Rheumatic Fever. BYWATERS, E. G. L., and THOMAS, G. T. (1961). *Brit. med. J.*, **1**, 1628. 5 figs, 15 refs.

The course of rheumatic fever in hospital in patients treated by bed rest alone and not given prophylaxis has been studied, and the degree of carditis related to other features of the attack. Prolonged raised temperature and sedimentation rate were more closely related to carditis than the sleeping pulse, but in severe attacks persistent tachycardia was a constant feature and carried a poor prognosis. Anaemia and loss of weight were uncommon and occurred only in the worst cases. Nodules were rare without heart disease, but were present in a quarter of those with slight carditis and in half of those with severe carditis.

The course in hospital in some patients treated by bed rest has been compared with that in others who were given 6-week courses of ACTH, cortisone, or aspirin, together with prophylactic sulphonamide. The two groups were comparable in most respects, although (*a*) they were not run concurrently; (*b*) only the drug-treated series was given prophylaxis; and (*c*) the latter had less heart disease at the start. Arthritis, temperature, and sedimentation rate subsided more slowly in the bed-rest series, but temperature was similar in the two by the fourth week, arthritis by the sixth week, and sedimentation rate by the eighth week; the rapid subsidence of activity in some of the bed-rest cases was striking. There was little difference in changes in cardiac status in the two groups, except in the development or disappearance of soft (Grade 1-2) murmurs, and this may have no important effect on the residual heart state 5 years later.

A third group of 47 cases was treated with 12-week courses of either cortisone or salicylate and did no better than those who had salicylate, cortisone, or ACTH for only 6 weeks.

Conclusions are drawn on the role of bed rest, salicylate, and steroids in the management of the disease. In many cases bed rest with salicylates to control fever and joint pain suffices, but in a few with severe attacks and cardiac enlargement delta-steroids are indicated and salicylates are potentially dangerous since they predispose to pulmonary complications.—[*Authors' summary.*]

Correlation of Population Age with Recovery Rates of β-Haemolytic Streptococci and Serological Responses: Relationship to Rheumatic Fever. STREITFELD, M. M., and SASLAW, M. S. (1961). *J. infect. Dis.*, **108**, 270. 1 fig., 18 refs.

In this investigation reported from the University of Miami School of Medicine, Florida, the recovery rate of β-haemolytic streptococci from throat cultures and the serological responses to these organisms were studied in three different age groups of apparently healthy subjects —800 elementary school children aged 6 to 9 years, 801 junior high school children aged 12 to 15 years, and 1,815 adults. Throat swabs were taken from all subjects and samples of blood from the adults. Streptococcal isolation rates were found to vary inversely with age. Group-A β-haemolytic streptococci were isolated from 14·4 per cent. of the children aged 6 to 9 years, from 7·9 per cent. of those aged 12 to 15, and from 2·2 per cent. of the adults. The pattern was similar for isolation of other β-haemolytic streptococci. There was no significant seasonal fluctuation. Group-C and Group-G β-haemolytic streptococci were found to be far commoner in the throats of children than in those of adults.

The average serum antistreptolysin-O (ASO) titre in the adults was between 71 and 74, but in those whose throat swabs were positive the average titre was 115 to 146. In an earlier study of other groups of children in Miami, the average ASO titre was found to be approximately 100. The lower average ASO titre in adults was considered to be due to a higher streptococcal carrier

rate in the children. These results generally parallel the higher incidence of acute rheumatic fever in children.

John Lorber.

Duration of Activity in Acute Rheumatic Fever. FEINSTEIN, A. R., and SPAGNUOLO, M. (1961). *J. Amer. med. Ass.*, **175**, 1117. 4 refs.

The duration of rheumatic activity was studied in 265 children and adolescents (aged 4 to 17 years) admitted to Irvington House, Irvington-on-Hudson, New York, with recent rheumatic fever. Rheumatic activity was considered to have ended when the temperature and sleeping pulse rate were normal, the erythrocyte sedimentation rate (uncorrected Wintrobe value) was 20 mm. per hour or less, and the response to the serum C-reactive protein test was negative. Abnormalities in temperature and pulse rate were regarded as significant only if they had been present for 3 consecutive days. Other clinical signs of rheumatic activity did not occur unless there were changes in temperature and pulse rate or in the results of laboratory investigations. Abnormalities in pulse rate or temperature usually subsided before the results of laboratory tests became normal. Therefore, cessation of rheumatic activity usually depended on the time when both the E.S.R. and the result of the C-reactive protein test became normal and remained normal after steroid and/or salicylate therapy was stopped.

The mean duration of activity in the entire group was 109 days; it was longer in patients with valvular involvement than in those without. In 31 patients originally treated with suppressive drugs, clinical rebounds occurred which were not treated; the mean duration of activity in this group was 79 days in patients with no valvular involvement and 112 days in those with valvular involvement, figures which were almost identical with those for similar patients whose entire attack had been untreated. The authors state that this was an unexpected finding which "suggests that the total duration of rheumatic activity remains essentially the same in most patients—rebound or no rebound, treatment or no treatment—so long as the original course of therapy is not given for a period of time longer than the natural course of the original inflammation".

C. E. Quin.

Rebound Phenomenon in Acute Rheumatic Fever.

I. Incidence and Significance. FEINSTEIN, A. R., SPAGNUOLO, M., and GILL, F. A. (1961). *Yale J. Biol. Med.*, **33**, 259. 3 figs, 22 refs.

II. Treatment and Prevention. SPAGNUOLO, M., and FEINSTEIN, A. R. (1961). *Yale J. Biol. Med.*, **33**, 279. 6 figs, 22 refs.

These papers record observations on the incidence, significance, treatment, and prevention of the rebound phenomenon in acute rheumatic fever as observed in children admitted to Irvington House, Irvington-on-Hudson, New York, from July, 1956, to August, 1958, at various stages of an attack of rheumatic fever. Originally 265 consecutive patients with unequivocal attacks of rheumatic fever were studied. A rebound was defined as the reappearance of clinical or laboratory features of rheumatic activity after they had originally subsided in the absence of any intercurrent Group-A streptococcal infection. The rebounds were subdivided into four groups:

(1) Slight "laboratory" rebound with the appearance of C-reactive protein (C.R.P.) and/or an erythrocyte sedimentation rate (E.S.R.) of 21 to 30 mm. in one hour;
(2) Significant "laboratory" rebound with a marked rise in titre of C.R.P. and/or an E.S.R. over 30 mm. in one hour;
(3) Slight clinical rebound with laboratory indications of a rebound together with fever;
(4) Significant clinical rebound with laboratory indications and one or more of the following clinical criteria—rise in sleeping pulse rate for three consecutive days, joint symptoms or signs, appearance of diastolic murmur of pericardial friction, development of congestive heart failure, and appearance of nodules or erythema marginatum.

The incidence of rebounds was studied with reference to the treatment the patient had received and the severity of the original attack. Of those receiving no specific therapy (34), no rebound occurred in 22 and a laboratory rebound (slight in six, significant in six) in twelve, but none developed clinical rebounds. Of the 106 patients treated with salicylates, 52 had no rebound, 44 had a laboratory rebound (slight in 15, significant in 29), and ten had a clinical rebound (slight in one, significant in nine). Of the 77 children treated with steroids alone, 25 had no rebound, 26 had a laboratory rebound (slight in 14, significant in 12), and 26 had a clinical rebound (slight in three, significant in 23). Of the 48 patients who received both salicylates and steroids, 21 had no rebound, fourteen had a laboratory rebound (slight in eight, significant in six), and thirteen had a clinical rebound (slight in four, significant in nine). No patient without clinical involvement of the heart in the original attack showed signs of heart disease in the rebound, but evidence of new heart disease appeared in ten out of 35 clinical rebounds occurring in patients with valvular involvement in the initial attack. Clinical rebounds occurred more frequently in those with carditis in the original attack. No rebounds occurred in patients treated with salicylates for more than 8 weeks. But, in those treated with steroids, the longer the drug was given, the more likely was a rebound to occur. To explain these findings it is suggested that suppressive medication (in which steroids are the most potent agent) "prevents the dispersion of rheumatic inflammation and that the accumulated residual inflammation thus appears in the form of a rebound when the suppression is reduced or stopped. The severity of the rebound will depend upon how much inflammation was present initially, how much of it was suppressed by the therapy, and how much remains afterwards".

In an attempt to determine the best forms of treatment and prevention of rebounds, an additional 150 children admitted consecutively from September, 1958, to August, 1959, were added to the above group, making a total of 415 consecutive admissions with definite evidence of rheumatic fever. Of these, 64 developed one or more clinical rebounds, 100 rebounds occurring in all. Laboratory rebounds had no clinical effects, always subsided spontaneously, and needed no treatment. In patients with no initial valvular involvement, clinical rebounds did not produce cardiac manifestations. In patients with valvular involvement, but no significant cardiac enlargement, the rebounds sometimes resulted in the appearance of new murmurs but no more severe cardiac effects. In both these groups, when the rebound was treated with suppressive agents, it was often followed by an additional rebound when the therapy was stopped. This was less likely to happen if the rebound was treated with salicylates than if it was treated with steroids. Rebounds could be prevented by not using anti-inflammatory agents in the initial attack or by treating it with salicylates alone for more than 8 weeks. In patients initially treated with steroids the incidence and severity of rebounds could be reduced by adding salicylates and continuing these for several weeks after the steroid therapy was stopped. However, in the group of patients with severe cardiac involvement in the initial attack, as judged by significant cardiac enlargement, rebounds might be associated with pericarditis, further increase in heart size, or congestive failure. If there were no cardiac features in the rebound it subsided spontaneously, but it frequently recurred if treated. No specific therapy for the primary rebound in this group seemed to reduce the occurrence of secondary rebounds. In a few patients "chronic" rheumatic activity of prolonged duration appeared, characterized by clinical rebounds not subsiding spontaneously and apparently unrelated to previous suppressive treatment. *C. Bruce Perry.*

Acute Articular Rheumatism in Children. (Le rhumatisme articulaire aigu chez l'enfant.) FORÊT-KESTLICHER, C., and GEUBELLE, F. (1961). *Rev. méd. Liège*, **16**, 301. 53 refs.

Q-Tc Interval in Rheumatic Fever. (O valor do Q-Tc na febre reumática.) PUIG, A., and DE VASCONCELOS, E. M. (1961). *Arch. bras. Cardiol.*, **14**, 41. 12 figs, 18 refs.

Cutaneous Manifestations of Rheumatic Fever. (Manifestazioni cutanee della malattia reumatica.) ARTOM, M. (1961). *Fracastoro*, **54**, 121.

Contribution to Experimental Studies on Rheumatic Fever. RAŠKA, K., ROTTA, J., and BEDNAR, B. (1961). *Path. Microbiol.*, **24**, 207. 8 figs, 10 refs.

Bacteriological Studies of Cardiac Tissues obtained at Autopsy from Eleven Patients dying with Rheumatic Fever. WATSON, R. F., HIRST, G. K., and LANCEFIELD, R. C. (1961). *Arthr. and Rheum.*, **4**, 74. 13 refs.

Community Plan by an Official and Voluntary Agency for Patients with Rheumatic Fever. BROWNELL, K. D., LOSTY, M. A., and O'SHAUGHNESSEY, H. M. (1961). *Amer. J. publ. Hlth*, **51**, 250.

Operation of a Co-operative State-wide Rheumatic Fever Prevention Program. SPINELLI, N. P. R., BROWN, H. A., and LAVNIKEVICH, N. J. (1961). *Amer. J. publ. Hlth*, **51**, 256. 3 refs.

Administrative Phases of a Rheumatic Fever Prophylaxis Program on a State-wide Basis. DEAN, C. (1961). *Amer. J. publ. Hlth*, **51**, 261.

Relation between the Serum Mucoprotein Level and C-reactive Protein, Weltmann's Band, and the Erythrocyte Sedimentation Rate in Rheumatic Fever. (Relacion de la mucoproteinemia con la proteina C-reactiva, banda de Waltmann y eritrosedimentacion en la fiebre reumatica.) BIDOGGIA, H., RODRIGUE, C., ALMONACID, E., BLANES, P., and LACOUR, J. J. (1960). *Pren. méd.* (*La Paz*), **47**, 3069. 14 figs, 19 refs.

Protein-Bound Hexoses, Glucosamine, and Other "Acute Phase Reactants" in Rheumatic Fever. ENGLESON, G., and LINDBERG, T. (1960). *Acta rheum. scand.*, **6**, 267. 3 figs, 27 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Observations on the Clinical Course and Treatment of One Hundred Cases of Still's Disease. SCHLESINGER, B. E., FORSYTH, C. C., WHITE, R. H. R., SMELLIE, J. M., and STROUD, C. E. (1961). *Arch. Dis. Child.*, **36**, 65. 9 figs, 32 refs.

The first part of this paper deals with the manifestations and complications of Still's disease in 100 patients (forty boys and sixty girls) followed up for 15 years at The Hospital for Sick Children, Great Ormond Street, and University College Hospital, London. The age at onset was most frequently "well below 5 years". In eighteen of the children systemic manifestations preceded joint involvement for varying periods of time, the average being 4 months. Fever tended to persist for a long time, even for years, and might have a peculiar periodicity. A rash, which was observed in forty patients, was usually associated with leucocytosis and lymphadenopathy; a leucocytosis of 30,000 cells per c.mm. with 80 to 90 per cent. neutrophil polymorphonuclear leucocytes occurred in 44 of the patients. In fourteen, minor injury had preceded the onset of the disease. Of particular interest was the occurrence of laryngeal stridor in three patients, one of whom required tracheotomy, and of a sterile necrotic area in a biceps muscle—a previously unreported

complication. Another unusual finding was that of osteolytic lesions of the skull in association with nodule formation; biopsy examination of subcutaneous tissue in the vicinity showed degeneration of collagen with fibrinoid changes. There was regression with steroid therapy. Dermatomyositis was present in three children, two of whom had subcutaneous nodules. In a further patient chorea with carditis developed 5 months after the onset of rheumatoid arthritis.

In the second part of the paper the management of patients with Still's disease and the long-term effect of steroid therapy are discussed. The basic regimen was rest followed by physiotherapy and graded activity. The authors state that with this regimen spontaneous remission may occur quite early, although it may not be maintained; there was a relapse in eleven such patients in the present series. Steroid therapy was instituted when simple measures failed; of 63 patients treated, sixty received steroids systemically and three by intra-articular injection. The initial dosage, which was high, was gradually reduced to a maintenance dose of 50 to 75 mg. daily, which was continued until it could be tapered off. The duration of treatment varied, but in the majority of patients 18 months was adequate, a finding which contrasts markedly with the duration of treatment of adults. More than one course of steroid therapy was necessary in some patients because of relapse. There were five deaths, two from the disease and three from intercurrent infections. Rapid improvement was observed with steroid therapy both in the acute phase of the disease and in the effect on the joints. Osteoporosis, particularly of the vertebral column, was seen in eight patients. This complication was likely to develop if the child was already osteoporotic at the start of therapy; however, no neurological complications were noted and recalcification was observed when administration of steroids was discontinued.

The authors consider that steroid therapy should be instituted when systemic disease or severe joint disturbance persists after several weeks, since the best results and often complete recovery are most likely with early treatment. *B. M. Ansell.*

Rheumatoid Arthritis of the Crico-arytenoid Joint. GROSSMAN, A., MARTIN, J. R., and ROOT, H. S. (1961). *Laryngoscope* (*St. Louis*), **71**, 530. 7 figs, 8 refs.

Laryngeal complications developing in the course of rheumatoid arthritis are rarely diagnosed during the patient's lifetime, though extensive changes may be demonstrable in the crico-arytenoid joint at necropsy. At the Montreal General Hospital, 55 patients with rheumatoid arthritis were closely questioned and underwent examination of the larynx by the authors. Of these, seventeen had some symptoms referable to the larynx. On mirror examination eighteen patients showed some evidence of crico-arytenoid arthritis, but nine of these had no laryngeal symptoms. In five out of eleven consecutive patients with rheumatoid arthritis who were examined *post mortem*, there was evidence of rheumatoid involvement of the larynx, but only two of these patients had had any laryngeal symptoms during life.

The authors discuss the question why this condition is so often unrecognized. On examination of the larynx there may be redness and swelling of the mucosa over one or both crico-arytenoid joints, but in the authors' series this finding was noted only rarely. In some cases the joint becomes disorganized and ankylosed in a deformed position, while fixation of one or both true vocal cords may occur in the midline position. Fixation of one cord in the midline will not produce stridor or severe hoarseness and in a bedridden patient who has no need to exert himself, this may even be true with bilateral fixation. Vocal change is not a common finding in these cases. Other symptoms that might be expected to be present, but are more often absent, are persistent sore throat, a feeling of "something sticking in the throat" after swallowing, and dysphagia. Even when symptoms and signs of laryngeal disease are present in a case of rheumatoid arthritis, they may not necessarily be due to involvement of the crico-arytenoid joint. Darke and others (*Brit. med. J.*, 1958, **1**, 1279; *Abstr. Wld Med.*, 1958, **24**, 441) reported that most of five cases of midline fixation of the cords clinically due to arthritis were proved at necropsy to be due to paralysis of the recurrent laryngeal nerve, while in one case the real cause was a laryngeal carcinoma. Other conditions to be excluded in differential diagnosis are the oedema of the area that may follow irradiation for carcinoma, laryngeal injury during endoscopy or endotracheal intubation for anaesthesia, prolonged feeding by nasal tube, and occasionally upper or lower respiratory tract infection with suppuration of or around the joint.

Stridor due to bilateral fixation of the vocal cords may necessitate surgical treatment in the form of tracheotomy or arytenoidectomy and cord lateralization. Some patients with rheumatoid arthritis have such deformity of the fingers that they may find it difficult to attend to a tracheotomy orifice; for these in particular lateralization of the cord or arytenoidectomy is useful. The authors point out that in some cases arthritic change can make indirect examination of the larynx impossible. [In such an event endoscopy must be considered.] The histories of the five cases which came to necropsy are given in full and a further case is mentioned in which routine *post mortem* examination of the crico-arytenoid joints in a patient who died of scleroderma revealed unsuspected non-suppurative arthritis. This suggests that such arthritis may occur in conditions other than rheumatoid arthritis.

[This is a valuable paper.] *F. W. Watkyn-Thomas.*

Effect of Short-Wave Diathermy on Radio-Sodium Clearance from the Knee-Joint in the Normal and in Rheumatoid Arthritis. HARRIS, R. (1961). *Arch. phys. Med.*, **42**, 241. 7 figs, 5 refs.

The rate of removal of radioactive sodium from a tissue is a quantitative measure of local circulation, and similarly the rate of clearance from the knee joint has

been shown to be closely related to circulatory changes. At the Devonshire Royal Hospital, Buxton, the author has used this technique to study the knee-joint in normal subjects and patients with rheumatoid arthritis and reports the effect of short-wave diathermy. Rheumatoid knees were graded 0, 1, or 2 according to the degree of clinical activity of the joint.

There was an average increase in clearance rate of 97 per cent. in the normal knee-joint after 20 minutes' heating with short-wave diathermy. The rheumatoid joints showed initial clearance rates similar to normal joints for Grades 0 and 1, but for Grade 2 (major involvement) the average initial clearance rate was 100 per cent. greater than the normal, demonstrating the presence of hyperaemia. After 20 minutes' diathermy joints of Grades 0 and 1 showed an average increase in clearance of 60 per cent., but those of Grade 2 showed an average reduction of 25 per cent., though the individual results varied considerably. The latter effect is similar to the effect of intra-articular hydrocortisone. This reduction of the hyperaemia of an active rheumatoid joint provides some rationale for using diathermy. *J. B. Millard.*

Anaesthetic and Post-operative Hazards in Rheumatoid Arthritis. GARDNER, D. L., and HOLMES, F. (1961). *Brit. J. Anaesth.*, **33**, 258. 3 figs, 17 refs.

In five patients with rheumatoid disease, respiratory difficulty during anaesthesia or unexpected post-operative death occurred. It is emphasized that such patients may be difficult subjects for the induction of anaesthesia on account of arthritis and ankylosis of the small joints of the larynx, of the cervical spine, and of the temporomandibular joints. In the same way the maintenance of adequate respiratory excursions during anaesthesia may be impeded by ankylosis of the costovertebral joints. Because of these manifestations of rheumatoid disease grave respiratory complications may be precipitated in the post-operative period. Following operation, the occurrence of interstitial pneumonia in rheumatoid arthritis may delay recovery. Particularly careful and continuous observation of these patients is necessary.

In other cases with rheumatoid arthritis, apparently straightforward operative procedures are followed by unexpected death. The high incidence of severe amyloidosis may determine a poor response to anaesthetic and analgesic drugs and may in part account for these fatalities. Further, it is becoming increasingly evident that unsuspected and potentially dangerous infection may remain latent in joints which are the sites of rheumatoid arthritis. There is reason to suppose that such patients have an altered response to infections to which, in spite of their characteristically hyperplastic reticulo-endothelial systems, they exhibit abnormally low resistance.—[*Authors' summary.*]

Association of Hashimoto's Thyroiditis and Rheumatoid Arthritis. BUCHANAN, W. W., CROOKS, J., ALEXANDER, W. D., KOUTRAS, D. A., WAYNE, E. J., and GRAY, K. G. (1961). *Lancet*, **1**, 245. 35 refs.

In this investigation undertaken at the Western Infirmary, Glasgow, to determine if there was possibly a relationship between rheumatoid arthritis and Hashimoto's thyroiditis, the authors studied 31 female and three male patients with Hashimoto's thyroiditis, 73 patients with rheumatoid arthritis, and a large control group consisting of 179 women attending various clinics, 125 diabetics, and 54 patients with dyspepsia.

Of the 31 women with Hashimoto's thyroiditis, diagnosed on the basis of a goitre and a positive precipitin reaction, or histologically, five had arthritis resembling rheumatoid arthritis in that it was characterized by a positive Rose-Waaler reaction and radiological joint changes, while a further three patients had a positive Rose-Waaler reaction, but no other evidence of rheumatoid arthritis, and one with a negative Rose-Waaler reaction had equivocal signs of rheumatoid arthritis. One of the three male Hashimoto patients had rheumatoid arthritis and a positive L.E. test. In contrast, only two of the 179 female control patients had rheumatoid arthritis. Although the zinc sulphate turbidity was considerably raised in four of the six patients with Hashimoto's thyroiditis, the γ-globulin level was never above 1·4 g. per 100 ml. Of the 46 women with rheumatoid arthritis, the complement-fixation test with thyroid tissue was positive in twelve, of whom two were hypothyroid and also gave a positive precipitin reaction, but neither had a goitre. This incidence of positive complement-fixation reactions (26 per cent.) was significantly higher than the 27 found among the 244 female controls (11 per cent.). None of the 27 men with rheumatoid arthritis had clinical or serological evidence of thyroid disease, although six out of the 292 controls showed positive complement-fixation test results.

The authors conclude that there is a significant association between Hashimoto's thyroiditis and rheumatoid arthritis, and consider that this clinical association favours the view that autoimmunization may play a role in rheumatoid arthritis. *G. L. Asherson.*

Rheumatoid Arthritis and Hepatocellular Injury. [In English.] NETTELBLADT, E. (1960). *Acta rheum. scand.*, **6**, 256. 2 figs, 36 refs.

The author of this paper from Södersjukhuset, Stockholm, discusses the results of liver function tests carried out in 77 patients (22 male, 55 female), aged 18 to 64 years, suffering from rheumatoid arthritis. Analysis of the results did not reveal any apparent relationship between the activity of the disease and the serum level of either glutamic oxalacetic transaminase or ornithine carbamyl transferase. However, there was an increase in the serum level of the latter enzyme in seventeen cases, which was believed to constitute evidence of a slight degree of liver-cell injury. It was also considered that patients with increased enzyme activity gave a better response to treatment with gold compounds or phenylbutazone than did patients in whom the serum enzyme levels were normal. No side-effects of gold treatment were encountered. A correlation was established between the serum activity of the enzymes and a decrease in the erythrocyte sedimentation rate.

The author points out that liver injury may result

from gold and phenylbutazone therapy. As liver injury associated with icterus may produce remissions in cases of rheumatoid arthritis, it is possible that favourable results of gold therapy may be related to slight hepatocellular damage. *A. Garland.*

Cancer Arthritis and Rheumatoid Arthritis. STRANDBERG, B., and JARLOV, N. V. (1961). *Arch. phys. Med.*, **42**, 273. 3 figs, 2 refs.

Reference is made to the similarity between the early symptoms of rheumatoid arthritis and those of many forms of cancer—that is, in the prodromal or early stages of both diseases and particularly before gross radiological changes can be detected in the rheumatoid joints. The authors then review their findings in 53 patients with rheumatoid arthritis admitted to the Copenhagen County Hospital during a recent 5-year period, a group of 91 healthy subjects serving for purposes of comparison.

The sex ratio (39 females and 14 males) conformed to that in rheumatoid arthritis. The patients could be divided into two groups: in the first the response to Hyland's rheumatoid arthritis test was positive in 26 out of 27 (96·3 per cent.) of the patients and in the second the response was positive in one out of 26 (3·8 per cent.). The response was positive in five (5·4 per cent.) of the 91 controls. The serum antistreptococcal-hyaluronidase and streptolysin titres and the results of the streptococcal agglutination test in the first group closely approximated those found in other series of cases of rheumatoid arthritis, while the values in the second group corresponded more closely to those obtained in the controls. The serum alkaline-phosphatase concentration was over 10 units in all except two patients in the second group. Paper electrophoresis showed that the serum protein fractions in the second group deviated significantly from normal and from those in the first group, particularly in respect of α_2-globulin content, which was raised in every case. Continued observation of the patients in the second group revealed that the time the above findings were obtained all these patients were in the early stages of malignant disease at various sites, including cancer of the lung (five), uterus (five), and stomach (four).

The authors suggest that rheumatoid arthritis is not to be regarded as a disease *per se*, but as an arthritic manifestation of allergy to noxious products arising in various diseases of muscle and skin. They further suggest that the syndrome may be the first indication of malignant disease. *William Hughes.*

Electromyographic Investigations in Rheumatoid Arthritis. [In English.] HAUGE, T. (1960). *Acta rheum. scand.*, **6**, 287. 8 figs, 8 refs.

Electromyography was carried out at Rikshospitalet, Oslo, in five patients with rheumatoid arthritis. In a man aged 50 there was loss of muscle power due to rheumatoid arthritis of the right metacarpo-phalangeal joints. Slight atrophy of the interosseous muscles was also present, but the results of clinical tests revealed no evidence of neurological disease. On electromyographical examination of the first interosseous space, however, the fibrillation potentials indicated the presence of a peripheral motor neurone lesion. The changes were attributed to rheumatic inflammation of the tissues in the vicinity of a motor nerve. Another patient showed fibrillation potentials in the left anterior tibial muscle several months before pain and swelling developed in the knees. In the remaining patients pathological spontaneous activity in the muscle tissue was demonstrated before the signs and symptoms of joint disease had become apparent. One patient included in the series had rheumatoid arthritis associated with chronic rheumatic inflammation of the spinal cord and a degenerative lesion of the neuromuscular system. In four out of six control cases of rheumatoid arthritis fibrillation potentials indicated a lesion of the lower motor neurone, but it was not possible to correlate the findings with the presence or absence of muscle atrophy. *A. Garland.*

Electromyographic Changes in Rheumatoid Arthritis. STEINBERG, V. L., and WYNN PARRY, C. B. (1961). *Brit. med. J.*, **1**, 630. 19 refs.

This study was carried out at the Department of Physical Medicine, the London Hospital, on 93 patients with definite rheumatoid arthritis to determine whether electrodiagnostic investigations would throw any light on the cause of the muscular wasting which occurs in this condition. The disease activity was classified according to the method of Duthie and others (*Ann. rheum. Dis.*, 1955, **14**, 133; *Abstr. Wld Med.*, 1956, **19**, 64). The activity and range of movement of the neighbouring joint was noted, together with the degree of wasting and the power of the selected muscles, these being the small muscles of the hand, the deltoid, the biceps, and quadriceps. Intensity-duration curves were plotted for each muscle, an R.A.F. constant voltage stimulator being used, and electromyography, employing concentric needle electrodes and a GHS double-beam electromyograph, was then carried out on the same muscle. The electromyogram (EMG) was thought to give the most sensitive result, 79 (85 per cent.) of the patients showing electromyographic evidence of polymyositis in one or more muscles. The intensity-duration curves revealed partial denervation in 37 of the muscles showing electromyographic evidence of polymyositis and in two muscles with a normal EMG.

The authors discuss their findings in relation to previous work on biopsy specimens of wasted muscle in rheumatoid arthritis. They conclude that the changes are not caused by steroid therapy, that there is no constant relationship to wasting and weakness of the muscles and activity of the neighbouring joints, but that there is some relationship between the degree of disease activity and the present findings. *Kenneth Tyler.*

Study of the Use and Mode of Action of Synthetic Antimalarials in the Treatment of Rheumatoid Arthritis. (Étude sur l'emploi et le mode d'action des antimalariques de synthèse dans le traitement de la polyarthrite chronique évolutive.) LECAPÈRE, J., MONIER, H., BONHOMME, F., and DELAVILLE, G. (1961). *Rev. Rhum.*, **28**, 1. 22 refs.

The authors report the results obtained with synthetic antimalarial drugs in the treatment of 191 cases of rheumatic disease, mostly (156) of rheumatoid arthritis. A course lasted 4 to 6 weeks and some of the patients were given eight to twelve such courses. Of the various drugs tried it was found that for practical purposes two chloroquine-type products and a diguanide were the only ones that were effective and well tolerated. The drugs were given in doses of from 100 to 900 mg. a day, either alone or in combination with other agents such as corticosteroids, gold, aspirin, and "butazolidin" (phenylbutazone); it was found that chloroquine often helped to reduce the maintenance dose of these drugs. No way was found of predicting which product or combination of products would suit a particular patient best.

Of the 156 cases of rheumatoid arthritis treated, 100 were regarded as having shown a very good or good response, and twelve out of nineteen cases of ankylosing spondylitis responded similarly. True idiosyncrasy to chloroquine was rarely observed. Side-effects, usually in the form of digestive disturbances, occurred, but none were serious and all appeared to be reversible. The problem of intolerance was often solved by changing the drug. There was no evidence of any acquired resistance to chloroquine. The authors consider that the use of these drugs in the treatment of rheumatoid arthritis is well worth while; they are safe, cheap, effective, and in many cases their use permits of the reduction of the dose of other more powerful and more toxic agents to a safer level. *B. E. W. Mace.*

Palindromic Rheumatism. DAMES, R., and ZUCKNER, J. (1961). *Arch. interamer. Rheum.*, **4**, 18. 26 refs.

Treatment of Arthritis with Guanido-Amino-Peptidase. A Preliminary Report. WALLS, A. (1961). *J. Mich. med. Soc.*, **60**, 607. 2 refs.

Pyramidon Gentisate in Association with a New Analgesic in the Treatment of Rheumatic Joint Disease. (Il gentisato di piramidone in associazione con un nuovo analgesico nel trattamento delle reumoartropatie.) BRAY, E. (1961). *Clin. ter.*, **20**, 412. 8 refs.

Destructive Rheumatoid Arthritis (Arthritis Mutilans). (L'artrite reumatoide destruente.) CERVINI, C., and LUCHERINI, M. (1960). *Reumatismo*, **12**, 239. 25 figs, 32 refs.

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Pericarditis in Rheumatoid Arthritis. TARPLEY, E. L. (1961). *Arch. interamer. Rheum.*, **4**, 50. 61 refs.

Morbid Anatomy of the Heart in Rheumatoid Arthritis. (Les lésions anatomiques du coeur dans la polyarthrite chronique évolutive.) VIGNON, G., PERRIN, A., DURANT, J., TRUCHOT, R., and BERTRAND, J.-N. (1961). *Lyon méd.*, p. 113.

Analysis of Sounds from Normal and Pathologic Knee Joints. FISCHER, H., AND JOHNSON, E. W. (1961). *Arch. phys. Med.*, **42**, 233. 11 figs, 11 refs.

Synovial Puncture Biopsy. (Puntura-biopsia sinoviale.) ORABONA, M. L., SEMERARO, V., BIANCHI, P., and DE VITA, V. (1960). *Reumatismo*, **12**, 272. 8 figs, 11 refs.

Radio-humeral "Meniscus" and its Relation to Tennis Elbow. DE GÓES, H., and SILVA, O. (1960). *Arch. interamer. Rheum.*, **3**, 582. 8 figs, 8 refs.

Non-infectious Arthritis in Small Bones and Joints. SCALF, R. F., and LING, J.-T. (1961). *Arch. intern. Med.*, **107**, 23. 5 figs, 15 refs.

Transverse Lesion in a Patient with Juvenile Rheumatoid Arthritis caused by Subluxation of Some Cervical Vertebrae. DE BLÉCOURT, J. J., and VEENSTRA, S. M. (1960). *Acta rheum. scand.*, **6**, 251. 1 fig., 5 refs.

Spontaneous Tendon Rupture and Cervical Vertebral Subluxation in Patients with Rheumatoid Arthritis. PAGE, J. W. (1961). *J. Mich. med. Soc.*, **60**, 888. 22 refs.

Restoration of Rheumatoid Finger-joint Function. Interim Report on Trial of Prosthetic Replacement. FLATT, A. E. (1961). *J. Bone Jt Surg.*, **43A**, 753. 9 figs, 10 refs.

Reclamation of the Rheumatoid Hand. FLATT, A. E. (1961). *Lancet*, **1**, 1136. 2 figs, 13 refs.

Rehabilitation of the Rheumatoid Hand by Surgical Means. HENDERSON, E. D., and LIPSCOMB, P. R. (1961). *Arch. phys. Med.*, **42**, 58. 11 refs.

Surgical Treatment of the Rheumatoid Hand. HENDERSON, E. D., and LIPSCOMB, P. R. (1961). *J. Amer. med. Ass.*, **175**, 431. 5 figs, 18 refs.

Experimental Rheumatoid Arthritis in Rabbits. NORLIN, G. (1960). *Acta rheum. scand.*, **6**, 309. 12 figs, 13 refs.

(Osteo-Arthritis)

Interphalangeal Osteo-Arthritis characterized by Painful, Inflammatory Episodes resulting in Deformity of the Proximal and Distal Articulations. CRAIN, D. C. (1961). *J. Amer. med. Ass.*, **175**, 1049. 4 figs, 11 refs.

Among 23 cases of osteo-arthritis of the interphalangeal joints of the fingers recently investigated at Georgetown University Medical School, Washington, D.C., middle-aged women predominated, and in many cases a family history of the condition was elicited. In one family the changes in the hands were similar in mother and daughter; in another family two sisters presented almost identical manifestations.

The disease was characterized by acute episodes of pain associated with inflammation and eventual deformity of the proximal and distal joints. Redness, swelling, local heat, and tenderness on pressure were observed during the acute phase. When the swelling increased in size there was severe impairment of function, and radiographs showed osteophyte formation, progressive narrowing of the cartilage space, destruction of the epiphyseal bone, and subluxation of the digits. In fourteen cases the terminal interphalangeal articulations were primarily affected, but for the most part the disease soon extended to all the interphalangeal joints, including those of the thumbs. Osteo-arthritic changes were also observed in the cervical vertebrae. Other peripheral articulations remained free from the disease.

Differential diagnosis was required from the painless degenerative disease of the terminal interphalangeal joints and the painful inflammatory phase of rheumatoid arthritis of the proximal interphalangeal joints. Serological tests for the rheumatoid factor yielded negative results. As regards treatment, symptomatic relief was obtained from the intra-articular injection of hydrocortisone. *A. Garland.*

Facial Neuralgia and Osteo-Arthritis of the Temporomandibular Joint. RASMUSSEN, P. (1961). *Acta psychiat. scand.*, **36**, 483. 14 refs.

Surgical Treatment of Osteonecrosis of the Femoral Head. (Traitement chirurgical de l'ostéonécrose de la tête fémorale.) DEBEYRE, J., SÈZE, S. DE, and SCHLOGEL, G. (1961). *Rev. Rhum.*, **28**, 17-26. 9 figs.

(Spondylitis)

Juvenile Ankylosing Spondylitis. [In English.] EDSTRÖM, G., THUNE, S., and WITTBOM-CIGÉN, G. (1960). *Acta rheum. scand.*, **6**, 161. 8 figs, 21 refs.

Over a recent 3-year period three cases of juvenile ankylosing spondylitis were seen at the University Hospital, Lund, Sweden. The patients, boys aged 5, 8, and 12 years respectively at the time the condition was diagnosed, had pain in the back associated with pains in the hips, shoulders, or knees. *X*-ray examination revealed changes in the sacro-iliac joints typical of ankylosing spondylitis. The erythrocyte sedimentation rate was raised and the response to the sensitized sheep-cell test was negative in all three patients. The authors also describe nine cases of juvenile rheumatoid arthritis in which the cervical spine was involved. Of the nine patients, six had dislocation or subluxation between the atlas and the axis with erosions of the odontoid process; the remaining three had osseous fusion of the posterior vertebral segments of a varying number of cervical vertebrae which was associated in all three cases with narrowing of the intervertebral disks and in one with changes in the sacro-iliac joints.

The cases described are considered to show that morphologically and clinically there is no sharp dividing line between ankylosing spondylitis and rheumatoid arthritis. *C. E. Quin.*

Ankylosing Spondylitis: A Note on an Early Contribution from Guy's. ZORAB, P. A. (1961). *Guy's Hosp. Rep.*, **110**, 96. 1 fig., 14 refs.

Early Ankylosing Spondylitis: Its Diagnosis and Treatment. AGGAEWAL, M. L. (1961). *Indian J. Radiol.*, **15**, 68. 6 refs.

Intermittent Cervical Traction in Cervical Spondylarthrosis. (Tracción cervical intermitente en las espondilartrosis cervicales.) LOSADA L, M., and DUEÑAS, A. (1961). *Arch. interamer. Rheum.*, **4**, 36. 7 figs, 9 refs.

(Miscellaneous)

Psoriasis and Arthritis: Clinopathologic Study. REED, W. B., BECKER, S. W., ROHDE, R., and HEISKELL, C. L. (1961). *Arch. Derm.*, **83**, 541. 2 figs, 17 refs.

The clinical features in 86 cases of arthritis associated with psoriasis and the *post mortem* findings in sixteen of them are discussed in this paper from the University of Southern California School of Medicine, Los Angeles. Of the sixteen deaths, two were due to perforated peptic ulcer and one to coronary thrombosis, although a penetrating peptic ulcer was also present. Myocardial infarction was responsible for four further deaths, infection (pyelonephritis, bronchopneumonia, and septicaemia) for three, haemorrhage (pulmonary and oesophageal varices) for two, and adrenal insufficiency, secondary amyloidosis, suicide (in a patient with a steroid-induced psychosis), and perforation of the terminal ileum from aminopterin for one each. Steroids were being administered to eight of the sixteen patients at the time of death and complications from this led to peptic perforation, psychosis, uncontrolled staphylococcal infection, increased hypertension, and acute adrenal insufficiency. All the patients continued to have exfoliative psoriasis in spite of a high dosage of steroids.

Discussing complications in the series as a whole the authors state that of the 86 patients peptic ulcers developed in ten, osteoporosis in two, and active tuberculosis in two. One gained 100 lb. (45·35 kg.) in weight in a year. Triamcinolone caused the greatest number of complications; during treatment with this drug diabetes

mellitus developed in one patient, muscular weakness in three, and in one there was rupture of a pregnant uterus. The psoriasis exfoliated in five patients while they were receiving triamcinolone.

Electrocardiographic examination, which was carried out on 84 of the 86 patients, revealed abnormalities in fourteen patients under 50 years of age and in 22 of those over 50. Spondylitic heart disease was present in three patients and strongly suspected in two others. These patients apparently had more severe systemic disease, with iritis, urethritis, severe peripheral arthritis, and pustular psoriasis.

[The cases of spondylitis, pustular psoriasis, iritis, and urethritis would probably have been classified in Britain as cases of Reiter's disease; they indicate once more the possible interrelationship between this condition, psoriasis, and arthritis.] *Benjamin Schwartz.*

Pathogenesis of Osteoporosis. NORDIN, B. E. C. (1961). *Lancet*, **1**, 1011. 6 figs, 35 refs.

The author discusses some observations which suggest that primary osteoporosis may be due to a long-continued negative calcium balance. The work of Albright and the subsequent literature on the pathogenesis of osteoporosis are reviewed, and reference is made to reported experiments in animals which showed that calcium deprivation without deficiency of vitamin D produced osteoporosis. At the Western Infirmary, Glasgow, analysis of the dietary intake of 71 patients with primary osteoporosis and 96 healthy subjects revealed a significantly lower intake of calcium in the patients with osteoporosis than in the controls, an observation confirmed by workers in the United States. The author has found that whereas in healthy subjects 10 days on a low-calcium diet reduces the urinary excretion of calcium by at least 30 per cent., little or no fall in calcium excretion occurs in patients with osteoporosis. These and other observations emphasize his view that long-continued negative calcium balance is a factor in the aetiology of osteoporosis. Of a group of 46 osteoporotic patients given 6 g. calcium glyceryl phosphate daily for 12 months, 22 were completely free from pain, although there was no convincing radiological improvement.

I. McLean Baird.

Cardiac Lesions in Reiter's Disease. CSONKA, G. W., LITCHFIELD, J. W., OATES, J. K., and WILLCOX, R. R. (1961). *Brit. med. J.*, **1**, 243. 7 figs, 19 refs.

The acute arthritis which is an outstanding feature of Reiter's disease and thus suggests some resemblance to rheumatic fever has prompted several investigators to search for cardiac lesions. In this paper the authors describe, from St. Mary's Hospital, London, three cases of Reiter's disease, all in males, in which aortic incompetence subsequently developed. The first patient, a West Indian, having at the age of 29 contracted gonorrhoea, had his first attack of Reiter's disease at the age of 38, when he developed pericarditis and a harsh apical systolic murmur, the electrocardiogram (ECG) showing a prolonged P-R interval of 0·28 second. When he was seen 4 years later, there was evidence of aortic incompetence, the patient having, in the intervening period, had several attacks of polyarthritis (one of which was treated by corticosteroids) and one of gonorrhoea; the latter had responded to penicillin, but had been followed by a further attack of non-specific urethritis. The second patient also developed Reiter's disease after contracting gonorrhoea (in 1940 at the age of 27). When examined in 1959, having then been suffering from dyspnoea of effort for about one year, he was found to have aortic incompetence. The ECG showed the P-R interval to be 0·28 second. The third patient developed Reiter's disease 8 years after an attack (in 1927) of gonorrhoea, which was followed by recurrent attacks of iritis. In 1957, when he was 53, he was found to have aortic incompetence, the P-R interval being 0·24 second. He was observed for a further 3 years, during which time he has had two further attacks of iritis, but his cardiac condition remains unchanged.

The authors also describe the case of a woman aged 50 who died in cardiac failure due to aortic incompetence which had been first diagnosed 5 years previously. This patient had had transient arthritis, iritis, and cervicitis, but the diagnosis of Reiter's disease could not be definitely established. *Post mortem* examination revealed atheroma and thickening of the intima of the aorta and thickening of the adventitia with endarteritis, changes which are usually ascribed to the late effects of syphilis and rheumatic endocarditis. (The three male patients described were discovered as a result of a long-term study of 215 cases of Reiter's disease.)

H. F. Reichenfeld.

Calcium Metabolism in Osteoporosis: Acute and Long-term Responses to Increased Calcium Intake. HARRISON, M., FRASER, R., and MULLAN, B. (1961). *Lancet*, **1**, 1015. 26 refs.

The cause of osteoporosis, or "simple" atrophy of bone, is not known. Recent studies of calcium metabolism do not support the widely accepted hypothesis that osteoporosis results from defective osteoplastic activity. Studies are reported here which suggest that calcium deficiency is an important factor in many cases of postmenopausal and senile osteoporosis. Many patients with these forms of osteoporosis absorb and retain calcium abnormally avidly when on a high calcium intake in the form of supplements (calcium gluconate), and, moreover, may continue to retain it avidly for at least 3½ years.

Symptoms of the disease are relieved, and no further fractures take place. Therapy with calcium supplements, therefore, seems to be of value for many patients with osteoporosis.—[*Authors' summary.*]

Sulphinpyrazone in the Treatment of Arthritis associated with Hyperuricaemia. GLICK, E. N. (1961). *Proc. roy. Soc. Med.*, **54**, 423.

Hyperuricaemia may be an indication that chronic arthritis is gouty in origin, although there is not necessarily a history of acute gout and tophi may be absent.

If so, reduction of the blood uric acid level with a uricosuric drug might be expected to relieve symptoms by reducing tissue deposits of urates. This occurred in eight out of ten patients (eight males) who were treated for periods of at least 4 months with sulphinpyrazone in a dosage of 100 mg. four times daily. In all the patients the serum uric acid level was 6 mg. per 100 ml. or higher. Only two patients had had acute gout, but all had chronic joint symptoms. In two the response to the Rose test was positive. During treatment the serum uric acid level fell from a mean of 6·7 mg. per 100 ml. to 4·2 mg. per 100 ml., rising again after cessation of therapy. There was a dramatic relief of symptoms within a few weeks in two patients and more gradual but definite relief in six others. The only serious side-effect was diarrhoea, which necessitated withdrawal of the drug in one case.

J. A. Cosh.

Shoulder Arthrography. SAMILSON, R. L., RAPHAEL, R. L., POST, L., NOONAN, C., SIRIS, E., and RANEY, F. L., JR. (1961). *J. Amer. med. Ass.*, **175**, 773. 9 figs, 8 refs.

This report from the University of California, San Francisco, confirms the value of contrast arthrography of the shoulder as a means of confirming the accuracy of a clinical diagnosis of soft tissue lesions around the joint which had been established by previous workers, and adds certain further observations. In addition to showing a high correlation with the clinical findings, the preoperative radiological diagnosis in a series of 125 arthrograms was proved correct in the thirty shoulders subjected to operation. The technique as described may be performed on an out-patient basis with full aseptic precautions, using sodium diatrizoate as a contrast medium. The procedure is likely to be accompanied by mild discomfort following the injection, with soreness of the shoulder on the following day. In this series no infections of the joint occurred.

In a normal arthrogram the subscapularis bursa, with its prolongation beneath the coracoid process, is outlined. This communicates with the glenohumeral joint, where the articular cartilages on each side are seen as negative shadows between the medium and bone. The synovial reflection along the intrascapular portion of the long head of biceps fills inferiorly, to a level just below the transverse bicipital ligament, but no farther. The subacromial bursa, lying between the deltoid and the rotator cuff, does not fill unless the latter is torn. Such tearing was the most common lesion (seventy cases) seen in this study, being the result of either recent trauma or slow degenerative attrition. Radiographically the axillary view is particularly important, since abduction helps to force the medium through the defect. In four cases such tears were associated with tears of the long head of biceps, the contrast medium being seen to descend well down into the arm. Dislocation injuries cause ballooning of the capsule, and in cases of "frozen shoulder" the joint capacity is diminished. The authors consider the investigation to be of considerable value, and hope to enhance its value still further by the use of cineradiography.

R. O. Murray.

Neurotropic Rheumatism of the Upper Limb (Shoulder-Hand Syndrome). (Le rhumatisme neurotrophique du membre supérieur (épaule-main.) RAVAULT, P. P., and DURANT, J. (1961). *Rev. lyon. Méd.*, **10**, 1. 7 figs, bibl.

The first-named author with others described in 1946 (*Arch. Rhum.*, **6**, 129) a painful disorder of the upper limb which has since become known as the "shoulder-hand syndrome". The present report is based on a study of 52 cases of this disorder seen since 1952, of which 36 have been followed up for several years. The onset is usually marked by diffuse pain in one upper limb, the distribution of which does not suggest root pain. Several days later the hand of the painful limb becomes swollen and the shoulder stiff. Less usually the first sign may be a stiff painful shoulder, suggesting "scapulo-humeral peri-arthritis", or a painful swollen hand, this condition occasionally being so severe as to suggest a cellulitis or an attack of acute gout. At first the whole hand is moderately oedematous, the skin red, and the palm sweating. Attempted movement of the fingers is extremely painful and the fingers cannot be fully flexed. At a later stage trophic changes in the hand are prominent, the skin is cold, often cyanotic, thin, and smooth, and the nails striated and brittle, while the intrinsic muscles are atrophied. Small indurations in the palmar aponeurosis suggestive of early Dupuytren's contracture are common. A flexion deformity of the fingers follows, with greatly restricted interphalangeal and metacarpophalangeal movements. The shoulder also shows severe restriction of all movements, resembling at times the almost complete immobility of "frozen shoulder". The most common *x*-ray finding is osteoporosis, in some cases severe, affecting mainly the epiphyses of the fingers, the carpal bones, and the humeral head. This may be absent in the early stages, but is very marked in the stage of trophic changes. The joint spaces remain intact, and erosions never develop. As a rule the outcome is favourable, but recovery may be delayed for 6 months to one year, or even longer. Recovery may be complete, but quite often there are minor sequelae such as an inability to extend the fingers. Uncommonly, severe disability from a stiff shoulder and loss of grip persists.

The aetiology of the syndrome is unknown, but among the suspected factors are trauma, either of the shoulder or hand, coronary thrombosis, certain affections of the pleura and lungs, lesions of the central nervous system, such as hemiplegia or cerebral tumour, and cervical spondylosis. The pathogenesis is uncertain. The authors favour the theory of a reflex sympathetic dystrophy, as suggested by Leriche.

Of many suggested methods of treatment, three are especially important:

(1) Immobilization, particularly if initial pain is very severe, when it may be permitted for a few days, but as soon as adequate relief is obtained active and passive movements must be begun.

(2) Stellate ganglion block, in experienced hands, may give a brilliantly successful result.

(3) Systemic corticosteroid therapy often brings

rapid relief, a short course of a few weeks being usually sufficient.

Some authorities hold that steroid therapy is not contraindicated in cases following myocardial infarction, but the authors' cardiological colleagues at Lyons do not consider that the risk, however slight, is justifiable.

[The paper contains a very full and useful bibliography.] *Kenneth Stone.*

Scapulohumeral Periarthritis and Hyperthyroidism. (Périarthrite scapulo-humérale et hyperthyroidie.) CHABOT, J. (1961). *Sem. Hôp. Paris*, **37**, 2247. 5 refs.

Reflex Scapulohumeral Periarthritis of Cervical Origin. (Périarthrite scapulo-humérale réflexe d'origine cervicale.) IMBERT, R., and ALLIES, P. (1960). *Rhumatologie*, **12**, 307.

Studies of the Painful Shoulder (Scapulohumeral Periarthritis).

III. Anatomical Study of the Senile Shoulder. (Études sur l'épaule douloureuse (périarthrite scapulo-humérale). III. Étude anatomique de l'épaule senile.) SÈZE, S. DE, RYCKEWAERT, A., WELFLING, J., HUBAULT, A., RENIER, J.-C., CAROIT, M., and POINSARD, G. (1961). *Rev. Rhum.*, **28**, 85 19 figs (13 in col.), 20 refs.

IV. Arthrography of the Frozen Shoulder. (IV. L'arthrographie de l'épaule bloquée.) SÈZE, S. DE, RYCKEWAERT, A., RENIER, J.-C., HUBAULT, A., WELFLING, J., CAROIT, M., and POINSARD, G. (1961). *Rev. Rhum.*, **28**, 279. 10 figs, 22 refs.

Chronic Degenerative Rheumatism and Ageing of the Locomotor System. (Rhumatisme chronique dégénératif et sénescence de l'appareil locomoteur.) BAUMGARTNER, P. (1961). *Cah. méd. Auvergne*, p. 123.

Ageing of Supportive Connective Tissues. (La senescenza dei connettivi di sostegno.) LUCHERINI, T., and CERVINI, C. (1961). *Reumatismo*, **13**, 1. 1 ref.

Regional Delineation of the Low Back Complex. KOPELL, H. P., and THOMPSON, W. A. L. (1961). *Rheumatism*, **17**, 38.

Relation between Chronic Glomerulonephritis and Chronic Polyarthritis. (Die Beziehungen zwischen chronischer Glomerulonephritis und chronischer Polyarthritis.) BRAUN, P. H. (1961). *Schweiz. med. Wschr.*, **91**, 174. 11 refs.

Gout

Heredity in Primary Gout. EMMERSON, B. T. (1960). *Aust. Ann. Med.*, **9**, 168. 6 figs, 21 refs.

There is considerable variation in the severity of gout and although its familial nature is recognized the extreme severity of certain cases compared with the mild form of the disease with onset during middle age has remained unexplained. In the first type, in which symptoms develop during or soon after puberty, recurrent acute attacks occur and the disease progresses rapidly to death from renal failure before middle age. From the Medical Professorial Unit of the University of Queensland, Brisbane Hospital, the author reports two family pedigrees containing persons homozygous for the gouty trait. In the first family one member developed severe primary gout and secondary renal disease at the age of 18 years. Both parents had hyperuricaemia and this was present in both the paternal and maternal lines of descent. Overt gout, however, was present in only one other member of the family, a cousin of the patient's mother. In the second family pedigree gout or hyperuricaemia could be traced through five generations, and as a result of the union of one of the gouty males with a hyperuricaemic family, four hyperuricaemic and gouty children were produced; three of these also had hypertension and two had evidence of impaired renal function.

In the first family the patient's renal disease was due to gout in itself, but the second family illustrates the association of hyperuricaemia and primary hypertensive vascular disease resulting in renal disease in a gouty subject. It is to be expected that the occurrence of an elevated serum urate level in both parents will result in an increased tendency to hyperuricaemia in the children. If the inheritance is by a dominant gene the children produced by two hyperuricaemic parents could be homozygous for this trait and would probably tend to manifest gout both with a greater severity than others and at an earlier age. If the inheritance is polygenic, that is, similar to that of other bodily characteristics such as height, a similar state would still be expected in the children of two parents with elevated serum urate levels.

J. Warwick Buckler.

Gout and the Haemoglobin Level in Patients with Cardiac and Respiratory Disease. LEWIS, J. G. (1961). *Brit. med. J.*, **1**, 24. 16 refs.

The relatively high frequency of gout in primary polycythaemia contrasts with the apparently low incidence in secondary polycythaemia, which the author regards as surprising. He has consequently investigated the incidence of gout in patients with polycythaemia secondary to congenital and acquired heart disease and to respiratory disease. During a survey at the Brompton Hospital for Diseases of the Chest, London, extending over 27 months there were 7,500 estimations of haemoglobin level, and only ninety patients were found to have a value of 120 per cent. or over (taking 100 per cent. as equal to 14·6 g. per 100 ml.). Gout was present in four of these patients, two of whom had congenital heart disease, one acquired heart disease, and one cor pulmonale. The author considers it important to recognize the association of gout with cyanotic heart disease, as otherwise the arthritis might be attributed to rheumatic

fever, vascular thromboses, or the embolic manifestations of bacterial endocarditis. *G. S. Crockett.*

Anturan in the Treatment of Gout. LUCEY, C. (1961). *Irish J. med. Sci.*, **6**, 113. 3 figs, 20 refs.

The treatment of five cases of primary gout with Anturan (sulphinpyrazone) is reported from the Royal Victoria Hospital, Belfast. There were four men and one woman aged between 33 and 72 years. The initial dose was 50 mg. (half a tablet) 6-hrly given with meals, increased where possible to 100 mg. 6-hrly after 4 or 5 days, the object being to lower the serum uric acid level to normal and to keep it there. To avoid renal lithiasis the urine was kept alkaline by the administration of sodium bicarbonate, 20 gr. (1·3 g.) 6-hrly. Except for a reduction in caloric intake for the obese patients no specific dietary regimen was followed. Acute attacks in the early weeks were treated with colchicine. One patient given hydrochlorothiazide for oedema of the ankles during treatment with anturan showed a startling rise in serum uric acid level.

The mean reduction in serum uric acid level was 43 per cent. All five patients felt improvement within a few weeks of starting treatment, including one patient with impaired renal function. Acute attacks of gout developed in four cases during the first few weeks of treatment, but, as the author points out, this is liable to occur with any uricosuric agent. On the other hand the occurrence of oedema of the ankles in two cases was attributed to the Anturan or the high sodium intake.

The author suggests that Anturan is the most effective uricosuric agent at present available, and recommends its use for the routine treatment of gout.

G. S. Crockett.

Sulphinpyrazone (Anturan) in the Treatment of Gout. PERSELLIN, R. H., and SCHMID, F. R. (1961). *J. Amer. med. Ass.*, **175**, 971. 11 refs.

Sulphinpyrazone (Anturan), a uricosuric analogue of phenylbutazone, was administered over an average period of 14 months to seventeen patients with gout, two of whom were in the chronic tophaceous stage of the disease, at the Medical Clinics of the Northwestern University Medical School, Chicago. The dosage was usually 400 mg. a day divided into four equal doses; colchicine was also given prophylactically in the initial months of treatment, but salicylates were prohibited.

Control serum uric acid values before treatment started averaged 8·7 mg. per 100 ml.; during therapy an average decrease of 37 per cent. to a mean value of 5·4 mg. per 100 ml. was obtained, the decrease ranging from 16 to 61 per cent. (A spectrophotometric uricase method was used for the serum analyses.) The frequency of acute attacks of arthritis fell after 5 months' treatment, and in the final 5 months no attacks at all occurred. The toxicity of the drug is stated to be low; two patients developed a maculopapular rash, one a mild leucopenia, and four had a dyspepsia which was relieved by taking the sulphinpyrazone with meals.

K. C. Robinson.

Trimethylcolchicinic Acid in the Treatment of Acute Gout. WALLACE, S. L. (1961). *Ann. intern. Med.*, **54**, 274. 1 fig., 22 refs.

This paper, from the State University of New York College of Medicine, the Jewish Hospital, and King's County Hospital, Brooklyn, New York, describes the results of treatment with trimethylcolchicine acid (TMCA) in 34 cases of acute gout. Treatment consisted in the oral administration of 5 to 16 mg. of TMCA, usually in a single dose and within 4 hours to 3 weeks of the onset of the attack.

Response was complete or nearly complete in 26 cases (76 per cent.), partial in four (12 per cent.), and absent in four (12 per cent.). Four patients showing no response and three showing partial response were later treated with colchicine and four proved to be resistant. There was a tendency for a poor response to occur in those cases in which treatment had been delayed. Prophylactic therapy with TMCA in doses of 1 to 3 mg. daily was carried out in seven cases. Although none of these patients developed an acute attack, it was considered that the period of observation (maximum 4 months) was too limited for an appraisal of the effectiveness of the drug as a prophylactic. Toxic effects were uncommon, with occasional mild nausea (one) and mild diarrhoea (two), and it is considered that TMCA compares favourably with colchicine for the treatment of acute gout.

Hewett A. Ellis.

Zoxazolamine in the Treatment of Gout. (La zoxazolamine dans le traitement de la goutte.) SERRE, H., SIMON, L., and CIURANA, A. (1961). *Rev. Rhum.*, **28**, 226. 6 figs, 18 refs.

This article from the Rheumatological Clinic, Montpellier, describes the use of zoxazolamine in the treatment of 27 cases of gout. In most cases the drug was given in doses gradually increasing up to 600 mg. a day, and daily blood and urine urate estimations were made so long as the patient was in hospital. Twelve patients admitted for other conditions were similarly treated for control purposes.

It was found that administration of the drug caused a reduction in blood urate level to normal and an increase in urate excretion in all the gouty subjects except one whose blood urate level before treatment was normal. In the control subjects, whose blood urate levels were also normal, the reduction under treatment was much less marked. In two gouty cases an appreciable reduction in the size of tophi was noted after 8 months of treatment. No side-effects of any significance were noted. Acute gouty attacks occurred in six cases during the early phase of treatment and in two of these the drug had to be withheld. Renal colic occurred in three cases after high dosage. Aspirin was shown to have an antagonistic effect on the uricosuric action of zoxazolamine but other uricosuric agents, such as phenylbutazone, probenecid, and "G 28315" [a phenylbutazone derivative], did not have this effect and can therefore be used in association with zoxazolamine with advantage: they may have a synergistic effect.

The authors conclude that zoxazolamine is a powerful uricosuric agent, of value in the treatment of chronic gout. Its effectiveness may lead to severe acute attacks at the beginning of treatment and for this reason dosage should be increased only gradually. *B. E. W. Mace.*

Borderline between Gout and Rheumatism: the Pseudo-gouty Form of Chronic Rheumatic Polyarthritis. (Aux frontières de la goutte et du rhumatisme: la polyarthrite chronique rhumatismale à form pseudo-goutteuse.) RAVAULT, P., LEJEUNE, E., and MAITRE-PIERRE, J. (1961). *Bull. Acad. nat. Med.* (*Paris*), **145**, 281. 26 refs.

The authors draw attention to certain patients with a form of rheumatoid arthritis which resembles gout and described twelve such cases occurring among a series of 800 patients with rheumatoid arthritis. These cases showed large subcutaneous nodules on the elbows, ulnar borders, fingers, and Achilles tendon. In general, nodules superficially resembling the tophi of gout were found anywhere that such tophi occur, with the exception of the ear. On *x*-ray examination the patients showed punched out "cysts" in the ends of the bones, also resembling those of gout. [The French word for this lesion is *géode*, but this term has already been used in English to designate a dilated lymph space.] The remaining findings in these cases were those of rheumatoid arthritis. *A. St. J. Dixon.*

The Gouty Kidney: Studies of 31 Cases of Renal Disease Associated with Gout. (Le rein goutteux: étude de 31 case de néphropathie associée à la goutte.) RICHET, G., ARDAILLOU, R., DE MONTERA, H., SLAMA, R., and BOUGAULT, T. (1961). *Presse med.*, **69**, 644. 9 figs, 16 refs.

The state of the kidneys in 31 patients with gout has been studied at the Hôpital Necker, Paris. Of 27 patients with typical chronic gout eleven had interstitial nephropathy secondary to uric acid stones and, of these eleven, seven presented with acute anuria due to obstruction of the outflow of the one functioning kidney, the other having been destroyed by similar episodes, while four presented with renal failure following a history of renal colic and the passage of stones, these patients having proteinuria, pyuria, and acidosis. Biopsy and necropsy examination in four of this group of eleven showed ascending nephritis, with tubular atrophy, cellular inflammatory reaction, fibrosis, and patchy glomerular involvement. Prevention of these changes of "gouty kidney" lies in the prevention and treatment of the formation of uric acid stones.

Another twelve of those with chronic gout had glomerular nephropathy but no calculi; here proteinuria and haematuria were more frequent than pyuria. Histological examination showed glomerular changes similar to those of glomerulonephritis at various stages of their evolution. In the remaining four cases of chronic gout there was intercurrent renal disease which was unrelated to the gout.

In three patients with no previous history of gout who developed the typical joint involvement secondary to renal failure there was glomerulonephritis, cystic disease of the pyramids, and polycystic disease respectively. The remaining case of the 27 was one of acute renal failure due to acute leukaemic infiltration of the kidneys and here also secondary gout developed.

The study of the plasma levels and urinary excretion of uric acid, urea, and creatinine confirmed the established view that chronic gout is not due to a renal defect, and it is suggested that even in renal failure the secondary gout may be due to a mechanism other than failure of renal excretion of urates. *T. B. Begg.*

Identification of Urate Crystals in Gouty Synovial Fluid. MCCARTHY, D. J., and HOLLANDER, J. L. (1961). *Ann. intern. Med.*, **54**, 452. 5 figs, 6 refs.

The nature of the crystals observed in synovial fluid from patients with gout and the frequency of their occurrence were studied at the University of Pennsylvania School of Medicine, Philadelphia. The fluid was examined by polarized light microscopy and a uricase digestion test was carried out on the crystals which were found to be negatively birefringent with extinction on the long axis. Urate crystals from a subcutaneous tophus were seen to behave similarly under polarized light microscopy.

Urate crystals were identified by polarizing microscopy in aspirated synovial fluid from fifteen out of eighteen patients with gout and by ordinary microscopy in fluid from only eleven of the eighteen patients. The crystals in fifteen positive samples and in two out of fourteen control samples from patients without evidence of tophi were specifically digested by uricase. On two occasions ordinary microscopy showed crystals that were not urate crystals. It is suggested that the concentration of urate in synovial fluid during an acute attack of gout is higher than that in the serum. In the authors' view examination of synovial fluid under a polarized light microscope should be a standard diagnostic procedure for gout.
J. E. Page.

Renal Biopsy in Gout. GREENBAUM, D., ROSS, J. H., and STEINBERG, V. L. (1961). *Brit. med. J.*, **1**, 1502. 3 figs, 14 refs.

The association of renal disease with gout is well recognized, but the pathogenesis of the kidney disorder has not been clearly defined. This study of renal biopsy specimens, reported fron the London Hospital, was designed to determine if very early lesions could be identified and if they could be correlated with the clinical state of the patients. Renal biopsy was performed on eleven men and one woman, aged 40 to 69 years, with a history of attacks of gouty arthritis ranging from 4 to 38 years. Renal function tests were also carried out. Only two of these patients were known to have evidence of renal impairment, but eight others were found to have proteinuria and/or impairment of renal function and six had disorders of renal structure.

The study provided no conclusive information about the production of gouty nephropathy. It is thought that possibly the earliest renal lesion is slowly progressive tubular damage accompanied by interstitial reaction. In time tubular atrophy would develop with or without coincidental infection and produce the final picture of "interstitial nephritis". *A. W. H. Foxell.*

Effects of Sulphinpyrazone on the Blood Level and Excretion of Uric Acid in Fifty Hyperuricaemic Patients with Gout during Thermal Diuretic Treatment. (Effets de la sulfinpyrazone sur l'uricémie et l'excretion de l'acide urique chez hyperuricémiques goutteux au cours d'une cure thermale de diurèse. Comparaison de l'action chez les goutteux simples et de celle chez les goutteux tophiques.) MUGLER, A. (1961). *Presse méd.*, **69**, 1072. 18 refs.

Hyperuricaemia and Acute Gouty Arthritis precipitated by Thiazide Derivatives. ARONOFF, A., and BARKUM, H. (1961). *Canad. med. Ass. J.*, **84**, 1181. 5 figs, 22 refs.

Colchicine and its Analogs in Gout: A Brief Review. HARTUNG, E. F. (1961). *Arthr. and Rheum.*, **4**, 18. 8 figs, 23 refs.

A Gallery of Gout: Being a Miscellany of Prints and Caricatures from the 16th Century to the Present Day. RODNAN, G. P. (1961). *Arthr. and Rheum.*, **4**, 27, 176. 32 figs.

Surgery of Gout in the Upper Extremity. STRAUB, L. R., SMITH, J. W., CARPENTER, G. K., JR., and DIETZ, G. H. (1961). *J. Bone Jt Surg.*, **43A**, 731. 10 figs, 28 refs.

Leg Ache: A Symptomatic Indication of Irregular Gout. PEPPER, H., and MANN, L. (1961). *Ann. intern. Med.*, **54**, 267. 6 refs.

Theoretical Concepts and Practical Applications of Hepatocatalase in the Treatment of Chronic Gout. (Concepts théoriques et applications pratiques de l'hépatocatalase dans le traitement de la goutte chronique.) BARCELÓ, P. (1961). *Scalpel* (*Brux.*), **114**, 435. 31 refs.

One Year's Experience with Hepatocatalase in the Treatment of Gout. (Une année d'expérience avec l'hépatocatalase dans le traitement de la goutte.) BARCELÓ, P., SANS SOLA, L., and PUIG MUSET, P. (1961). *Scalpel* (*Brux.*), **114**, 595.

Action of Hepatocatalase on Metabolic Disturbance in Gout. (Acción de la hepatocatalasa sobre el trastorno metabólico de la gota.) BARCELÓ, P., SANS-SOLA, L., and PUIG MUSET, P. (1961). *Rev. argent. Reum.*, **26**, 26.

Pararheumatic (Collagen) Diseases

Intradermal Hypersensitivity in Systemic Lupus Erythematosus. BENNETT, J. C., and HOLLEY, H. L. (1961). *Arthr. and Rheum.*, **4**, 64. 2 figs, 15 refs.

The authors, at the Medical College of Alabama, Birmingham, have studied the reaction of patients with systemic lupus erythematosus to intradermal injections of normal leucocytes. A positive reaction, maximal at 24 hours, occurred in fifteen out of seventeen cases of systemic lupus erythematosus, but in only two out of forty cases of rheumatoid arthritis and in one case of rheumatic fever out of 26 cases of other diseases tested as a control. Histological studies of the injection sites were made in a number [unstated] of cases of systemic lupus erythematosus and control cases. In the former an inflammatory exudate of polymorphs and mononuclear cells tending to localize around blood vessels, degenerative nuclear changes, and some fibrinous transudate were seen, whereas biopsies from the control subjects showed only mild oedema with little inflammatory reaction. *M. Wilkinson.*

Renal Manifestations of Systemic Lupus Erythematosus; a Clinical and Pathological Study of 90 Cases. SOFFER, L. J., SOUTHREN, A. L., WEINER, H. E., and WOLF, R. L. (1961). *Ann. intern. Med.*, **54**, 215. 15 refs.

This paper from the Mount Sinai Hospital, New York, describes the renal manifestations which occurred in 56 of ninety patients suffering from systemic lupus erythematosus (S.L.E.). All the patients had characteristic clinical and laboratory evidence of S.L.E., including a positive reaction to the L.E. cell test, and all those with renal involvement had persistent proteinuria, while 88 per cent. had haematuria, 63 per cent. pyuria, and 70 per cent. casts in the urinary sediment. Renal involvement was more frequent and severe in the younger patients, 35 instances occurring in those less than 30 years, of whom sixteen died and twelve others had azotaemia. Of 21 patients over 30 years, eight died, nine had minor renal damage, and four had azotaemia. The longer the disease continued without renal involvement, the less likely was this to occur. Clinical features in the patients with renal involvement included the nephrotic syndrome (37 per cent.), hypertension (44 per cent.), oedema (35 per cent.), and abnormal fundi (30 per cent.). Pathological examination of the kidney in nineteen cases showed that the degree of histological damage correlated with the severity of the clinical manifestations and the prognosis, but not with the blood urea level or 2-hr phenolsulphonphthalein excretion values.

Treatment with various steroids (for example, cortisone, initial dose 200 to 300 mg., maintenance dose 50 to 100 mg. daily; prednisone, initial dose 40 to 60 mg., maintenance dose 10 to 25 mg. daily) in doses sufficient to control other symptoms of the disease failed to control the renal manifestations. Thus, 26 of the 56 patients with renal involvement died, whereas none of the 26 patients without renal involvement who were followed up did so.

The study illustrates the serious prognosis in patients with renal involvement in S.L.E., even when treated with steroids. The authors suggest that more intensive and prolonged therapy might have favourably influenced the prognosis. *Hewett A. Ellis.*

Lupus Erythematosus: a 5-year Follow-up of 77 Cases. MARTEN, R. H., and BLACKBURN, E. K. (1961). *Arch. Derm.*, **83**, 430. 3 refs.

In a previous paper (*A.M.A. Arch. Derm.*, 1956, **73**, 1; *Abstr. Wld Med.*, 1956, **20**, 62), the authors reported haematological abnormalities in just over half of 66 cases of chronic discoid lupus erythematosus, in five out of six cases of generalized discoid lupus erythematosus, and in all five systemic cases seen in the Sheffield area between 1948 and 1952. The present paper deals with the clinical and haematological states of the same patients after a further 5 years of observation. Of the original 77 patients, ten have died (but in only one case was death attributable to the lupus erythematosus), a further nine could not be traced, and one patient had moved from the area, leaving the 57 patients which are the subject of the present survey.

Of 51 chronic discoid cases (38 female, 13 male), in seventeen the disease was clinically inactive, seventeen showed active and scarred lesions, and seventeen active lesions only. Three of the four cases of generalized discoid disease and the two cases of subacute disseminated lupus erythematosus still showed active and scarred lesions. Haematological abnormalities were demonstrated in thirty cases of chronic discoid, two of generalized discoid, and two of subacute disseminated disease. These consisted of microcytic hypochromic anaemia (three), leucopenia (four), lymphopenia (four), leucocytosis (one), thrombocytopenia (six), raised erythrocyte sedimentation rate (25), and cold agglutinins (two). In addition, L.E. cells were found in the peripheral blood in four cases of chronic discoid, two of generalized discoid, and both cases of subacute disseminated lupus erythematosus. In all, thirty cases of chronic, two of generalized, and two of disseminated disease had some haematological abnormality.

In discussing their findings the authors comment on the increased number of chronic discoid cases which have become inactive, and they note again that there were no obvious clinical differences between the cases with abnormal and those with normal haematological findings. No cases of chronic discoid disease developed systemic lupus erythematosus, and only one case became generalized. In the period under review there was no evidence to suggest that cases of chronic discoid lupus erythematosus with haematological abnormalities are more likely to develop systemic manifestations.

Benjamin Schwartz.

Lymphadenoid Goitre and the Syndrome of Systemic Lupus Erythematosus. WHITE, R. G., BASS, B. H., and WILLIAMS, E. (1961). *Lancet*, **1**, 368. 4 figs, 22 refs.

The authors, at the London Hospital, have investigated the presence of antinuclear factor in the serum of forty patients with lymphadenoid goitre, using a histological technique with a fluorescent antibody. In 28 of these patients the diagnosis had been confirmed by histological examination of the thyroid gland. Positive control sera were obtained from cases of systemic lupus erythematosus, and negative controls from an antenatal clinic and from routine blood donors. Other tests performed were complement fixation and precipitin tests and haemagglutination of tanned sheep erythrocytes sensitized with purified thyroglobulin.

Of the forty cases, five gave a positive result for antinuclear factor; all five cases were in females aged from 48 to 82 years. In two of the cases no other disease was present; one had signs of systemic lupus erythematosus (S.L.E.) 2 years after a positive serum reaction for antinuclear factor had been elicited, while in another case there were features suggesting this disease; and one had rheumatoid arthritis and rheumatic heart disease.

It is suggested that, while these findings are not regarded as supporting the idea that lymphadenoid goitre is a direct manifestation of S.L.E., they may indicate that a small subgroup of cases of lymphadenoid goitre arises in patients with S.L.E. who have a special propensity to form antibodies generally. *B. M. Ansell.*

Study of the Mechanism by which Quinacrine Inhibits L.E. Cell Formation. NEILSON, N., and LANSBURY, J. (1961). *Amer. J. med. Sci.*, **241**, 700. 2 figs, 13 refs.

Working at the Temple University School of Medicine, Philadelphia, the authors have studied the inhibition of L.E. cell formation in cases of systemic lupus erythematosus (L.E.) by quinacrine (mepacrine) in the hope that an understanding of this mechanism might shed light on the antirheumatic action of the drug.

Electrophoretic studies on serum incubated with quinacrine suggested no firm binding of the drug by protein, and ultraviolet-light studies of blood films after exposure to quinacrine showed a considerable concentration of the drug in leucocyte cytoplasm, with a little in the nuclei, and none in the erythrocytes. The addition of quinacrine to suspensions of normal leucocytes in normal plasma almost abolished pseudopod formation and phagocytosis by leucocytes when the drug concentration was 0·4 mg. per ml. or more.

Prior treatment of potent L.E. serum with quinacrine followed by dilution to below 0·4 mg. per ml. did not interfere with L.E. cell production, suggesting that quinacrine does not inactivate the L.E. serum factor. Nor did exposure of a suspension of leucocyte nuclei to quinacrine prevent their conversion to L.E. bodies and subsequent phagocytosis when potent L.E. serum and leucocytes were added. This suggests that quinacrine does not inhibit the union of L.E. serum factor and nucleoprotein. Only when the concentration of quinacrine reached 0·4 mg. per ml. was L.E. cell formation inhibited and the authors believe this to be due to inhibition of phagocytosis. This drug concentration is far above therapeutic levels and the study does not help to explain the antirheumatic action of quinacrine.

M. Wilkinson.

Clinical and Serological Features of Visceral Lupus Erythematosus. (Klinik und Serologie des viszeralen Lupus erythematodes.) DÖRNER, M., ENDERLIN, M., SPIEGELBERG, and MIESCHER, P. (1961). *Dtsch. med. Wschr.*, **86**, 378; 431. 2 figs, 43 refs.

The authors have compared, at the Medical and Rheumatic Clinics of the University of Zürich, the clinical and serological features in 48 patients with systemic lupus erythematosus (S.L.E.) with those in 48 cases of rheumatoid arthritis (R.A.) and five in which the diagnosis lay between these two conditions. The criteria for the diagnosis of the different disorders are described. Of the patients with S.L.E., 75 per cent. were female, compared with only 58 (4 per cent.) of those with R.A. There was some selection of the patients with rheumatoid arthritis, in that the more severe cases tended to be sent for examination.

Clinically, fever, tiredness, gastro-intestinal disturbances, cardiac symptoms, involvement of the lungs, kidneys, and serous membranes and enlargement of the liver, spleen, and lymph nodes were all more frequent in the patients with S.L.E.; a typical skin rash occurred in 35·2 per cent. of these patients, but joint deformity was noted in only about 27 per cent. Morning stiffness occurred in both groups. In the S.L.E. group there was a high incidence of mental symptoms which sometimes mimicked schizophrenia or severe depression. In some cases, however, the disease ran a very mild course and occasionally lesions histologically resembling those of Henoch-Schönlein purpura were seen; marked haemolytic anaemia was found in two cases. Although anaemia and leucopenia were commoner in the patients with S.L.E., 32 of them had leucocyte counts above 4,000 per c.mm. The L.E. test was positive in 75 per cent., as compared with 9·5 per cent. of the patients with R.A. Homogenization of the nucleus without phagocytosis was noted in 13·1 per cent. of the latter, but in only 2·5 per cent. of the former.

Performance of the very sensitive conglutinin modification of the complement fixation test showed that 42·5 per cent. of the patients with S.L.E. developed antibodies against histone, nucleoprotein, and notably deoxyribose nucleic acid (D.N.A.), but only 4·1 per cent. of those with R.A. did so; on the other hand, 32 per cent. of the latter reacted with one of these antigens as compared with 10 per cent. of the patients with S.L.E. Thus multiple autoantibody production was a feature of the lupus patients. The Coomb's consumption test, using nuclei as antigens, was positive in 97·5 per cent. of the lupus patients, but in only 34·2 per cent. of the rheumatoid group; the figures for a positive latex fixation reaction were 42·5 and 89·6 per cent. respectively. Antibodies against thyroglobulin were found in 21 per cent. of the lupus patients. Although the formation of antibody against nucleoprotein and D.N.A. was characteristic of S.L.E. nearly all the known autoantibodies have been found in some cases of this disease, reflecting the loss of immunological self-recognition.

In the differential diagnosis of S.L.E. it is noted that septicaemia, disseminated malignant disease, Hodgkin's disease, rheumatic fever, and scleroderma must be excluded. Difficulty arises when the typical rash is absent and the L.E. test is negative. When all tests for antibody against nuclei are negative the diagnosis of S.L.E. is rarely tenable. Differentiation from rheumatoid arthritis may be impossible in the absence of pathognomonic biopsy findings characteristic of S.L.E. Particularly puzzling are those cases in which withdrawal of cortisone leads to exacerbation of rheumatoid arthritis with visceral involvement.

The authors come to the conclusion that in spite of their apparent similarity, these two diseases are clearly distinct in their clinical picture and the pattern of their serology. They suggest, however, that rheumatoid arthritis may provide a favourable soil for the development of systemic lupus eyrthematosus. *G. L. Asherson.*

Occurrence of L.E. Cells and Hematoxylin Bodies in the naturally occurring Cutaneous Lesions of Systemic Lupus Erythematosus. WILSON, R. M., ABBOTT, R. R., and MILLER, D. K. (1961). *Amer. J. med. Sci.*, **241**, 31. 7 figs, 23 refs.

Although haematoxylin bodies have frequently been described as occurring in necropsy and biopsy material from cases of disseminated lupus erythematosus (D.L.E.), L.E. cells have apparently not previously been recorded in the naturally occurring lesions of D.L.E. They have, however, been found in the fluid of blisters artificially induced on the skin of patients with D.L.E. and in blood taken from a finger after constriction. The present communication from the Edward J. Meyer Memorial Hospital, Buffalo, New York, describes two cases. In the first case a woman with a confirmed diagnosis of D.L.E. had some cutaneous lesions at the elbow, one of which, on biopsy, showed many typical L.E. cells extravascularly, as well as haematoxylin bodies. The second case, of apparently uncertain diagnosis, showed, in a biopsy of clinically normal skin, some basophil bodies 10 to 33 μ in diameter. No other specific lesions were described in the biopsy specimen. The known factors required for the formation of L.E. cells are briefly discussed. *G. Loewi.*

Erythema Nodosum. JAMES, D. G. (1961). *Brit. med. J.*, **1**, 853. 5 figs, 7 refs.

Collected by the author between the years 1950 and 1959, 170 cases of erythema nodosum, predominantly in adults, have been investigated with particular regard to aetiology. The general pattern demonstrated a spring incidence, a female preponderance (3 : 1), and a maximum frequency in the age group 20 to 29 years. Lesions on the arms were present in 7 per cent. of cases, while all the patients developed lesions on the legs. There was no deviation from the clinical description originally propounded by Willan in 1808, although many patients had constitutional signs such as fever for a few days before the eruption, and 62 per cent. had varying degrees of polyarthralgia. Radiographs, Mantoux and depot

tuberculin tests, the Kveim test, electrophoresis of the serum proteins, and estimations of the erythrocyte sedimentation rate and serum antistreptolysin titres demonstrated that in 74 per cent. of cases the outbreak was associated with clinical or laboratory signs of definitive sarcoidosis, and a similar aetiology was likely in a further 9 per cent., although the strict criteria set forbade definite inclusion in the group. In 13 per cent. of cases the lesions developed in association with infection (streptococcal in twelve cases, tuberculous in four, pneumonia in three, and acute colitis and dental abscess in one each). In the remaining 4 per cent. investigation failed to reveal a possible cause.

It was felt that the use of the Kveim test offered the best opportunity of establishing an aetiological diagnosis. The lesions of erythema nodosum usually clear rapidly without treatment within 6 weeks, although in a few cases in this series they persisted for as long as 20 weeks. Recurrences were infrequent, occurring only in 8 per cent., and usually within 3 months. The radiographic and other manifestations of sarcoidosis cleared completely, usually in 6 months, although a few were prolonged as long as 6 years. Only one patient with iridocyclitis suffered lasting damage from the attack. In view of the excellent results the use of steroids, which might interfere with a little-known immune reaction, is not indicated in treatment. *Allene Scott.*

Episcleral Nodules and Erythema Nodosum. McCarthy, J. L. (1961). *Amer. J. Ophthal.*, **51**, 60. 21 figs, 44 refs.

A review of the reported cases of ocular lesions associated with erythema nodosum is given; the most common were scleral and conjunctival nodules and uveitis. A case of erythema nodosum and episcleral nodules is described. Biopsy of the latter showed a histological picture resembling the Aschoff body. The inflammatory reaction was considered to be an allergic response, probably excited by the streptococcus, and the author concludes that these reactions should not be classified among the collagen diseases. *M. C. Handscombe.*

Collagen Disease and the Chronic Biological False Positive Phenomenon. Catterall, R. D. (1961). *Quart. J. Med.*, **30**, 41. 4 figs, 15 refs.

A series of 54 patients (36 women and 18 men) attending or referred to the Whitechapel Clinic of the London Hospital were found to have persistent non-syphilitic reactions to the classic serological tests for syphilis. They had no past history or clinical evidence of syphilis, and the treponemal immobilization test gave negative results in all cases. These patients were observed for one to 5 years and were subjected repeatedly to haematological studies, estimation of the plasma total protein and albumin and globulin levels and of the serum cholesterol level, and investigation of their peripheral blood for the presence of L.E. cells.

During observations, six of the women developed systemic lupus erythematosus with L.E. cells in the peripheral blood, one dying, while one of the men died of periarteritis nodosa. In addition, nine women and five men developed discoid lupus erythematosus or other possible collagen diseases without L.E. cells, and twelve women and four men had various haematological abnormalities such as anaemia or a persistently raised erythrocyte sedimentation rate. The incidence of sensitivity to penicillin in the whole series was high (20 per cent.). As in other reported series, the chronic biological false positive reaction appeared to be of more serious prognostic importance in women than in men. The finding of such a reaction should lead to full clinical investigation and prolonged follow-up. *G. W. Csonka.*

Vasculitis, Mast Cells, and the Collagen Diseases. Smyth, C. J., and Gum, O. B. (1961). *Arthr. and Rheum.*, **4**, 1. 9 figs, bibl.

Purpura is a frequent complication in patients suffering from rheumatoid arthritis who have been treated with high doses of adrenocortical steroids. The authors of this paper from the University of Colorado School of Medicine, Denver, describe the clinical and pathological findings in two such cases, and then speculate on the basis of the necrotizing angiitis, commenting on the fact that the lesion is perivascular as well as mural and intramural. Attention is drawn to the prevalence of mast cells in the neighbourhood of the blood vessels and in the loose connective tissues of certain structures and organs. There is evidence in the literature that the mast cell has been implicated in the production of heparin (Jorpes, 1936), hyaluronic acid (Asbøe-Hansen, 1950), histamine (Riley, 1953), and serotonin (Benditt, 1955), and it is suggested that cells which produce such potent biological substances must have some important part to play in the chain of events known as the inflammatory reaction. *R. E. Tunbridge.*

Blood Lipids in Psoriasis. The Effects of "Lipostabil". Enticknap, J. B., Ryan, C. C., and Lansley, T. S. (1961). *Brit. J. Derm.*, **73**, 99. 9 refs.

Stating that it has been reported that "dietary deficiency of certain polyunsaturated fatty acids results in skin changes in rats not unlike those seen in human psoriasis" the authors describe a trial of these fatty acids in the treatment of six women with psoriasis, six others who received a placebo forming a control group. Most of the patients were given daily six capsules containing 320 mg. soya bean extract and 0·6 mg. pyridoxine, with 0·1 mg. α-tocopherol as an anti-oxidant; for the control group the placebo capsule contained lactose and α-tocopherol. The serum lipid content and lipid fractions were fully investigated before treatment, after a fast of 12 hours, and periodically during 3 months' observation. There was no significant difference between the two groups, no clinical response to the treatment, and the serum lipid levels, which were initially normal, did not change during or after the treatment. *S. T. Anning.*

Nodular Glomerulosclerosis: Clinico-pathological Correlation of Forty Advanced Cases. HENNIGAR, G. R., COHEN, R. J., and KATZ, H. P. (1961). *Amer. J. med. Sci.*, **241**, 89. 3 figs, 20 refs.

This paper from King's County Hospital, Brooklyn, New York, presents a re-evaluation of the relationship of renal nodular sclerosis (intercapillary glomerulosclerosis of Kimmelstiel and Wilson) to the course of diabetic disease. The authors studied only cases showing the more severe histological signs—that is, more than half out of a series of twenty glomeruli showing at least one nodule each, the nodules being fibrous, slightly cellular, and located in the intercapillary space. Cases showing only diffuse intercapillary sclerosis and sudanophilic nodules were excluded. Clinically, patients were considered to have acidosis if there had been a history of diabetic coma, ketonuria, or diminished CO_2-combining power.

Of 525 diabetics examined post mortem between 1950 and 1959, forty had kidneys presenting the picture of severe nodular sclerosis. Of these, nineteen had had acidosis. Hypertension had been present in most, and proteinuria in all, of the forty cases. There was no positive correlation with the incidence of pathological changes in the islets. The authors consider their findings to be at variance with the conclusion reached by others (Zubrod and others, *New Engl. J. Med.*, 1951, **245**, 518; *Abstr. Wld Med.*, 1952, **11**, 52) that acidosis is rare in diabetics showing Kimmelstiel-Wilson renal lesion.

G. Loewi.

The Heart in Scleroderma. ORAM, S., and STOKES, W. (1961). *Brit. Heart J.*, **23**, 243. 7 figs, 45 refs.

This report from King's College Hospital, London, and Stoke Mandeville Hospital, Aylesbury, describes the involvement of the heart in scleroderma in a personal series of 21 cases and in 28 cases found in the literature. There is a full review of previous work, which indicates that the heart is only rarely directly involved by the sclerodermatous process. The cardiovascular system may be affected by cor pulmonale as the result of lung involvement, by hypertension secondary to renal scleroderma, or by direct involvement of the heart muscle.

In generalized scleroderma the cardiac symptoms do not appear until late in the disease. They presage early deterioration and death, the average survival being 30 months after the onset of cardiac symptoms. The progress of the cutaneous disease and its relation to cardiovascular symptoms are extremely variable. Dyspnoea, congestive cardiac failure, gallop rhythm, and mitral valvular incompetence occur commonly. Abnormality of rhythm is rare, though atrial fibrillation and flutter do occur. Pain in the chest is a common symptom, though there is no evidence of coronary vascular disease at necropsy. Extensive pulmonary fibrosis may occur with minimal *x*-ray changes. Pulmonary function may be impaired either as a result of reduced ventilation from involvement of the skin and muscles or of impaired diffusion through an alveolar-capillary block. The kidney may be infiltrated with scleroderma and if this is extensive death occurs from renal failure. Hypertension is unusual and when it occurs is pre-terminal. Death from this cause may be precipitated by steroid therapy.

Radiological investigation shows an enlarged cardiac silhouette; less frequently interstitial fibrosis and cyst formation are seen in the lower lung zones, and pulmonary calcification has been reported. Spontaneous pneumothorax and pleural effusions may complicate the course of the disease. The authors point out that the finding of deposits of calcium scattered throughout the body in any case of obscure cardiopathy is of obvious importance since they may occur in scleroderma unaccompanied by other evidence of the disease. The commonest site is the fingers, especially near the tips, and although such patients usually have severe and obvious sclerodactyly the calcinosis is occasionally an unexpected finding on routine radiology. Although the electrocardiogram may be normal in sclerodermatous heart disease, non-specific changes were in fact found in 48 of the present 49 cases. The predominant changes were ventricular extrasystoles, prolonged P-R interval, right bundle-branch block, and T-wave changes. Changes typical of myocardial infarction in the absence of pain were considered to be suggestive of sclerodermal involvement.

The pathological changes in the heart, which, in about half the present cases, was increased in weight, are those of infiltration with collagenous tissue together with atrophy of the intervening heart muscle. The latter occurs without evidence of impairment of blood supply. Pericarditis is common and a verrucous endocarditis may occur. The lung shows fibrosis of the alveolar wall and obliteration of the capillaries. Changes secondary to spillover from the obstructed oesophagus may also be seen. Patchy changes are seen in the kidney, but opinion is divided as to whether involvement of the renal vessels is the prime cause for this as hyalinization of the glomeruli, with capsular thickening and the so-called wire-loop appearance, is also seen.

Treatment is unsatisfactory, though in the authors' experience life may be prolonged by the use of corticotrophin or steroids in high dosage. Care in their administration to patients with renal involvement is necessary, for while two of their patients improved, one died as a result of an exacerbation of renal failure.

J. S. Malpas.

Ocular Changes in Linear Scleroderma. SEGAL, P., JABLONSKA, S., and MRZYGLOD, S. (1961). *Amer. J. Ophthal.*, **51**, 807. 6 figs, 27 refs.

Report of a case of linear scleroderma *en coup de sabre* of the face. Sectoral atrophy of the mesodermal layers of the iris appeared on the side of the skin lesions within a few months of onset of the disease. Their nature indicated a neurotrophic origin, suggesting a connection between scleroderma and the nervous system which is specially distinct in linear scleroderma. The authors do not believe that linear scleroderma *en coup de sabre* is identical with Romberg's idiopathic hemiatrophy.

M. H. T. Yuille.

Electromyographic Findings in Scleroderma. HAUSMANOWA-PETRUSEWICZ, I., and KOZMINSKA, A. (1961). *Arch. Neurol.*, **4**, 281. 3 figs, 12 refs.

This study, reported from the School of Medicine, Warsaw, was based on the electromyographic examination of fourteen cases of diffuse scleroderma (including acroscleroderma) and twelve cases of morphoea. In the former group of patients, all females, 39 muscles, 28 in regions with sclerodermatous changes and eleven in apparently normal regions, were examined. In the four male and eight female patients with morphoea electromyograms were recorded from 28 muscles, of which thirteen were in regions of sclerodermatous change and fifteen were in uninvolved areas.

All the patients were examined clinically, and other investigations included capillaroscopy, measurement of sensory chronaxy and of skin electrical resistance, recording of intramuscular temperatures, and histopathological examination. In recording the electromyograms concentric needle electrodes were used, three electrodes being inserted into each of the muscles investigated at different points and the position of the needle tips repeatedly changed by 5 to 10 mm.

The authors tabulate their findings as follows:

(1) Spontaneous activity;
(2) Reaction to passive movement;
(3) Type of effort pattern;
(4) Intensity of polyphasia;
(5) Peak to peak amplitude;
(6) Mean potential duration.

The results indicated that the features characteristic of myogenic inflammatory lesions comprise a complex interference pattern. Thus disturbances of effort gradation, and low potentials of short duration with a high percentage of polyphasic potentials can be observed in diffuse scleroderma both in muscles underlying involved skin and in muscles distant from such areas. The decrease in potential duration was not only statistically significant, but very marked. In cases of circumscribed scleroderma the abnormal features were noted in muscles underlying the skin lesions, but nine out of fifteen distant muscles examined gave normal electromyographic patterns. *Kenneth Tyler.*

Ocular Changes in Periarteritis Nodosa. [In Danish.] SVANE-KNUDSEN, P. (1961). *Ugeskr. Laeg.*, **123**, 229. 15 refs.

A 47-year-old man with a general disease, probably a generalized periarteritis nodosa, had bilateral central scotomata and acutely increased intra-ocular pressure. The eyes improved on treatment with corticosteroids, but the disease was fatal within 3 years. *G. von Bahr.*

Fundus Aspects in Malignant Visceral Lupus Erythematosus and Periarteritis Nodosa. (Aspects du fond d'oeil rencontres au cours de la lupo-érythémato-viscérite maligne et de la péri-artérite noueuse.) CORDIER, J., SAUDAX, E., and MOURAUX, J.-M. (1960). *Bull. Soc. Ophtal. Fr.*, p. 518. 7 figs.

Preliminary Results with 1-(2-Benzylcarbamoylethyl)-2-Isonicotinoyl Hydrazine (Nialamide) in the Treatment of Various Rheumatic and Pararheumatic Disorders. (Primeiros resultados obtidos pelo uso de 1-(2-(benzilcarbamil) etil)-2-isonicotil hidrazina (Nialamida) em portadores de afecçoes reumáticas e parareumáticas diversas.) GAMARSKI, J. (1961). *Hospital*, **59**, 749. 5 refs.

Focal Infection in the Collagen Diseases. (La infeccion focal en las enfermedades del colageno.) MASELLI, F., ZAMPINI, S. J. L., PEREZ, A. A., and CHIMENTI, O. (1961). *Sem. méd. (B. Aires)*, **68**, 1278, 1300.

Angiopathy in Collagen Diseases. (Les angiopathies des maladies du conjonctif.) MARTIN, E. (1961). *Mal. Card.*, **2**, 1. 5 figs, 19 refs.

Changes in the Intramural Nervous Ganglia of the Heart in Collagen Diseases. (Alterazioni dei gangli nervosi intramurali cardiaci in corso di collagenosi.) SCALABRINO, R., and ROSSI, L. (1961). *Reumatismo*, **13**, 5. 6 figs, 7 refs.

Sclerodermal Heart Disease: Pathological and Clinical Observations. (La cardiopatia sclerodermica.) CURTARELLI, G., and PASQUARIELLO, G. (1960). *Reumatismo*, **12**, 260. 5 figs, 60 refs.

Scleroderma (Progressive Systemic Sclerosis): Nosological Aspects, Outlines of Special Histopathogenesis, and Aetiopathogenic Theories. (La scleroderma (Sclerosi sistemica progressiva): Aspetti nosologici, lineamenti di istopatogenesi speciale e prospettive etiopatogenetiche.) PENDE, G. (1961). *Arch. E. Maragliano Pat. Clin.*, **17**, 533. 20 figs (5 col.), bibl.

New Data on the Pathology of "True Scleroderma Kidney". URAI, L., MUNKÁCSI, I., and SZINAY, G. (1961). *Brit. med. J.*, **1**, 713. 9 figs, 5 refs.

Scleroderma and Pneumoconiotic Pulmonary Disease. (Sclérodermie et atteintes pulmonaires pneumoconiotiques.) BRUN, J., KALB, J. C., and FROMENT, A. (1961). *J. franç. Méd. Chir. thor.*, **15**, 397. 4 figs, 20 refs.

Diagnosis and Treatment of Lupus Erythematosus, Dermatomyositis, and Scleroderma, with Emphasis on Cutaneous Findings. WINKELMANN, R. K. (1961). *J. chron. Dic.*, **13**, 401. 5 figs, 18 refs.

Prognosis and Course of Generalized Lupus Erythematosus. (Über die Prognose un den Verlauf des generalisierten Lupus erythematodes.) ZISWILER, H. (1961). *Dtsch. med. Wschr.*, **86**, 1302. 1 fig., 8 refs.

Observations concerning the Electrophoretic Distribution of Proteins in Systemic Lupus Erythematosus. DÉCOURT, L. V., COSSERMELLI, W., and FERRI, R. G. (1960). *Arch. interamer. Rheum.*, **3**, 526. 24 refs.

Effect of 6-Mercaptopurine Administration on Antibody Production and Clinical Course in Systemic Lupus Erythematosus. LEE, S. L., MEISELAS, L. E., ZINGALE, S. B., and RICHMAN, S. M. (1961). *Arthr. and Rheum.*, **4**, 56. 1 fig., 14 refs.

Specificity of Passive Haemagglutination and Complement-Fixation Techniques in Diagnosing Systemic Lupus Erythematosus. JOKINEN, E. J., and MÄKITALO, R. (1960). *Acta rheum. scand.*, **6**, 297. 11 refs.

Total Exchangeable Potassium in Systemic Lupus Erythematosus with Reference to "Triamcinolone Myopathy". BENNETT, J. C., CLAYBROOK, J., KINSEY, H., and HOLLEY, H. L. (1961). *J. chron. Dis.*, **13**, 411. 41 refs.

Pleuro-Pulmonary Manifestations of Systemic Lupus Erythematosus. ALARCÓN-SEGOVIA, D., and ALARCÓN, D. G. (1961). *Dis. Chest.*, **39**, 7. 10 figs.

General Pathology

Comparative Studies of the Rheumatoid Factor and Tissue Auto-antibodies in Rheumatoid Arthritis. (Vergleichende Untersuchung von Rheumafaktor und Gewebsautoantikörper bei primär-chronischer Polyarthritis.) STEFFEN, C., ROSAK, M., and TATZREITHER, H. (1961). *Schweiz. med. Wschr.*, **21**, 178. 1 fig., 22 refs.

The authors, working at the Hanusch Hospital, Vienna, have performed the latex-fixation test, the latex-drop test, and the antiglobulin-consumption test on the sera of patients with rheumatoid arthritis. The latex-fixation and the latex-drop tests showed good agreement; thus the sera of 35 of 49 patients with rheumatoid arthritis gave a positive result by both tests and those of seven a negative result by both, a concordance rate of 86 per cent. In the sera of 42 patients with miscellaneous conditions, including three with hepatic cirrhosis, four with Waldenström's macroglobulinaemia, and nine with osteo-arthritis, seven gave a positive result by the drop test. These seven patients were suffering variously from rheumatic fever, cirrhosis, uraemia, osteo-arthritis, or Henoch-Schönlein purpura. It is noted that none of the titres in these seven cases was above 1 : 40, whereas in the patients with rheumatoid arthritis the titres ranged from 1 : 80 to 1 : 1,280.

The antiglobulin-consumption test was performed by mixing the serum with lyophilized homogenate of human pariarticular and joint capsule tissue. After washing, the ability of the tissue to reduce the titre of an anti-human globulin serum was measured. Of 62 patients with rheumatoid arthritis, the serum of 41 gave a positive result, only 27 being positive in both the antiglobulin-consumption and the latex-fixation tests. It is pointed out that the factor responsible for the antiglobulin-consumption test could be absorbed by lyophilized joint tissue without altering the titre in the latex-fixation test. The authors had earlier shown that lyophilized brain tissue was inactive. In conclusion they stress the rapidity of the latex-drop test and its good correlation with the latex-fixation test. They conclude that two different serum factors occur in rheumatoid arthritis and raise the question whether the rheumatoid factor combines *in vivo* with the factor responsible for the antiglobulin-consumption test. *G. L. Asherson.*

Rheumatoid Factor and the Pathogenesis of Rheumatoid Arthritis. MELLORS, R. C., NOWOSLAWSKI, A., KORNGOLD, L., and SENGSON, B. L. (1961). *J. exp. Med.*, **113**, 475. 24 figs, 21 refs.

The authors have previously shown (*J. exp. Med.*, 1959, **110**, 875; *Abstr. Wld Med.*, 1960, **28**, 54) that a fluorescein-labelled aggregated human gamma-globulin (F.A.A.G.) was a sensitive reactant for the detection of the 19S macro-globulin complex known as "rheumatoid factor" in preparation of cells and tissue sections. This further report from the Hospital for Special Surgery, New York, describes similar observations utilizing another fluorescent immune complex (F.I.C.) (rabbit antibody to bovine albumin). In this test 127 specimens of synovial and lymph-node tissue from nine cases of rheumatoid arthritis and 85 from twelve control patients without rheumatoid arthritis were subjected to examination. The specificity of the fluorescent staining attributable to the rheumatoid factor was confirmed by inhibition of the reaction by previous exposure to similar complexes without the labelled fluorescein element.

It was shown that a small proportion of the cells in the richly cellular inflammatory exudate stained with F.I.C., these being plasma cells, both immature and mature and also those of the Russell-body type. (A greater number of cells stained with F.A.A.G., however, than with the F.I.C.) Similar differentiation was obtained by variation of the inhibiting reagents. Two categories of cells in lymph nodes were found to contain rheumatoid factor detectable with F.I.C., namely, the germinal centre cells and the plasma cells; the former may be numerous in hyperplastic lymph nodes. None of the control specimens showed positive staining with the single exception of a specimen from a patient with Waldenström's macroglobulinaenia, which reacted positively with F.A.A.G. and with a fluorescent antibody for macroglobulin, but did not react with F.I.C. It is concluded that while there is much that is consistent with the hypothesis of the rheumatoid factor being an antibody directed to an altered human gammaglobulin and cross-reacting with rabbit gammaglobulin, the authors suggest an alternative explanation, namely, that there may be several rheumatoid factors directed against different antigenic components of aggregated human gammaglobulin, some of which are present also in the rabbit F.I.C. In an addendum to this paper they announce

the preparation of fluorescent reactants in contrasting colours by means of which differential staining of plasma cells can be produced, thus supporting at least a dual nature of cellular rheumatoid factor. *Harry Coke.*

Rapid Precipitation of the Rheumatoid Factor in a Solution of Boric Acid and Titration by the Agglutination Sensitized Human Erythrocytes. (Précipitation rapide du facteur rhumatoïde dans une solution d'acide borique et titrage par l'agglutination des hématies humaines sensibilisées.) BADIN, J., and LEVESQUE, H. (1961). *Rev. Rhum.*, **28**, 101. 25 refs.

A rapid and simple method of precipitating the rheumatoid factor from sera for testing by haemagglutination is described. It was found that if the serum was diluted in 20 volumes of 2 per cent. boric acid solution an adequate precipitate containing the rheumatoid factor could be obtained after 30 minutes. This fraction was shown to constitute, on average, 13·6 per cent. of the serum total protein content in sera from patients with rheumatoid arthritis. It is claimed that this method of separating the globulin fraction is superior to the use of citrate-phosphate buffer both by enabling a greater amount of precipitate to be obtained in a short time and also by giving a more clear-cut result in the subsequent haemagglutination test. It is suggested that this rapid and complete precipitation of the rheumatoid factor is due to a combination of boric acid with polysaccharides which are known to be present in quantity in the rheumatoid factor. *G. W. Csonka.*

Clinical Study of Serum Antinuclear Factor. WEIR, D. M., HOLBOROW, E. J., and JOHNSON, G. D. (1961). *Brit. med. J.*, **1**, 933. 39 refs.

This paper from the M.R.C. Rheumatism Research Unit, Canadian Red Cross Memorial Hospital, Taplow, describes the application of Coons's fluorescent antibody technique to the demonstration of an antinuclear factor (A.N.F.) in the serum of patients with systemic lupus erythematosus (S.L.E.) and certain other disorders. Sections of human infant thyroid tissue were incubated with test serum at 37° C. for 30 minutes and after careful washing were stained with a fluorescein *iso*cyanate or *iso*thiocyanate conjugate with anti-human-globulin serum. Under controlled conditions a nuclear fluorescence indicated a positive reaction for A.N.F. [It is stated that the positive nuclear fluorescence indicates an uptake of globulin from the test serum. Since some of the antisera used were directed against whole human serum, it is not clear which globulin component is being demonstrated.]

Positive A.N.F. reactions were obtained in 62 (98 per cent.) out of 63 cases of S.L.E., nineteen (14 per cent.) of 132 of rheumatoid arthritis, thirteen (13 per cent.) of 100 of Still's disease, and ten (13 per cent.) of 75 of discoid lupus erythematosus. Positive reactions were also obtained in 13 per cent. of 100 cases of thyroid disease and 39 cases of liver disease. The reaction was negative in 56 cases of rheumatic fever and in 131 of 133 normal subjects. It is concluded that, although in S.L.E. the A.N.F. reaction is persistently positive, a positive reaction is not in itself of diagnostic value.

The authors suggest that the A.N.F. in patients with S.L.E. may be the same as the factor responsible for the L.E.-cell phenomenon and they discuss the significance of the test from the diagnostic and aetiological points of view and in the light of Burnet's clonal theory. *Hewett A. Ellis.*

Latex-Fixation Test using British Latex and Bovine Gamma Globulin. PAYNE, R. B. (1961). *J. clin. Path.*, **14**, 309. 12 refs.

This paper from the Welsh National School of Medicine, Cardiff, records investigations into the use of bovine γ globulin and a British preparation of polystyrene latex particles in the latex-fixation test for rheumatoid arthritis. Initial investigations demonstrated that spontaneous agglutination occurred in a standard latex suspension with bovine γ globulin in two ranges of concentration—$3{\cdot}1 \times 10^{-1}$ to $9{\cdot}8 \times 10^{-4}$ g. per 100 ml. and $3{\cdot}9 \times 10^{-5}$ to $4{\cdot}9 \times 10^{-3}$ g. per 100 ml. All concentrations from 2·5 g. per 100 ml. to *nil* were tested and, with the exception of these specified ranges, no agglutination occurred. In the presence of serum from patients with rheumatoid arthritis agglutination failed to occur with concentrations of bovine γ globulin of $6{\cdot}3 \times 10^{-1}$ g. per 100 ml. and above. At concentrations between $6{\cdot}3 \times 10^{-3}$ and $7{\cdot}8 \times 10^{-4}$ g. per 100 ml., it was possible to obtain agglutination titres with a clear end-point. Prozoning did not occur as it did with concentrations of $4{\cdot}9 \times 10^{-5}$ g. per 100 ml. or below. A concentration of 5·0 mg. per 100 ml. was found to be the most satisfactory to give the highest titres with the majority of positive sera. Further experiments showed that the highest titres were evolved by bulk heating of the latex and γ globulin mixture and then adding it to the serum dilutions after cooling.

Duplicate tests were made on 300 specimens of serum using a standard latex test based on these principles and the sensitized sheep cell test as modified by Greenbury and Ball, with plastic agglutination trays. Assuming the result of the latex test to be positive with agglutination to a titre of 1 : 80 or greater, there was agreement in 264 of the 300 tests (88 per cent.). Some analysis is made of the cases giving divergent results, which, it is noted, included a number of cases of rheumatoid pneumoconiosis. The technique of the standard test evolved is set out in detail and shown to be inexpensive, easy, and quick to perform. The titres obtained by this latex technique showed no correlation with those of the sensitized sheep cell test. In an addendum the results of a comparison of this latex test and the Hyland R.A. test, which utilizes human γ globulin as the reactant are reported. Agreement in 135 of 141 cases (95·7 per cent.) is recorded. *Harry Coke.*

Studies on the Latex-Fixation Test. (Studien über den Latex-Fixations-test.) SEIFERT, H. (1960). *Z. Rheumaforsch.*, **20**, 26. 4 refs.

Discrepancies between the results of the Rose-Waaler test and those of the latex-fixation test have occasionally been noted by the author. This casts some doubt on the present concept that both of these tests depend on the presence of the rheumatoid factor in the serum. In a comparative investigation it was found that the results of the latex-fixation test were in close agreement with the L-agglutination reaction against streptococci and those of the Rose-Waaler test with the γ-globulin reaction. In absorption experiments in which the heterohaemagglutinins and the rheumatoid factor were removed from a rheumatoid serum the Rose-Waaler and γ-globulin reactions became negative, whereas the latex fixation and L-agglutination reactions remained unchanged. It is concluded that the Rose-Waaler and γ-globulin reactions demonstrate the presence of the rheumatoid factor and the latex fixation test depends on a factor which agglutinates streptococci. *G. W. Csonka.*

Erythrocyte in Rheumatoid Arthritis. I. A Method for the Detection of an Abnormal Globulin Coating. FINKELSTEIN, A. E., KWOK, G., HALL, A. P., and BAYLES, T. B. (1961). *New Engl. J. Med.*, **264**, 270. 1 fig., 17 refs.

The rheumatoid factor in serum has been shown to react with the agglutinate latex particles coated with polysaccharides such as heparin, chondroitin sulphate, and hyaluronic acid. The authors had shown also the binding of the rheumatoid factor with the polysaccharide dextran. This paper describes a study of the protein substance coating the erythrocytes of patients with rheumatoid arthritis and the removal of this substance by admixture with 3·6 per cent. dextran in physiological saline solution. After separation by centrifugation the supernatant was tested for agglutinating capacity by the standard latex-fixation test of Singer and Plotz. Initial saline washings of the erythrocytes never produced agglutinating capacity; the dextran washings, however, produced agglutination up to 1 : 64, with the majority at 1 : 4.

The erythrocytes of 196 patients out of 197 with classic rheumatoid arthritis produced positive agglutination. In further tests the number of positive results decreased with the grade of the disease, down to 65·2 per cent. in cases of "possible" rheumatoid arthritis. In 38 cases of definite rheumatoid arthritis in which the serum was negative with the latex and euglobulin latex-fixation tests, positive results were obtained by this method. Some positive results (35) were also obtained in a series of 92 cases of other "rheumatic disease syndromes", and nine positive results in a series of 141 non-rheumatic conditions. These results showed that the erythrocytes of patients with rheumatoid arthritis are coated with a protein substance which is similar to if not identical with the rheumatoid factor, and that this substance cannot be removed by saline, but is eluted by dextran, solutions of Fraction II, sialic acid, or dextrose.
Harry Coke.

Fluctuations of Free Amino-Acids in the Serum and Urine of Patients with Progressive Rheumatoid Arthritis. (Změny volných aminokyselin v séru a v moći nemonných s progresivni polyartritidou.) TRNAVSKÁ, Z., and SIT'AJ, Š. (1961). *Vnitrni Lek.*, **7**, 36. 30 refs.

The authors state that there is definite interference in the metabolism of free amino-acids in progressive rheumatoid arthritis, and report the results of an analysis by means of one-dimensional paper-chromatography of the amino-acid levels, after a known diet, in the serum and urine of 62 patients, fifty women and twelve men, with proved progressive rheumatoid arthritis and of 25 healthy individuals, fifteen women and ten men, who served as a control group. The methods are fully described. It was found that the serum levels of proline and histidine in the controls were within normal limits and did not vary. In the patients, however, there was a marked decrease in the serum levels of both proline and histidine, although the free amino-acid levels in the urine showed no marked changes. It was also noted that the average serum histidine level was lower in patients suffering from anaemia and the authors point out that histidine is an amino-acid which takes an active part in the formation of normoblasts. Finally, it was established that the decrease in serum levels of free proline and histidine correlated with the stage of the disease and also the degree of anaemia. *Paul Frankl.*

Contribution to the Study of Sjögren's Syndrome. FERREIRA-MARQUES, J. (1960). *Acta derm.-venereol. (Stockh.)*, **40**, 485. 1 fig., 16 refs.

In three cases of Sjögren's syndrome the author studied the histopathology of the glands and hairs of the axilla. Manifold rows of coiled apocrine glands showed atrophy and degeneration. Giant tubulae with amorphous and atonic walls were found. The cells showed degenerate mitochondria and a degenerate Golgi apparatus. The eccrine sweat glands showed a vacuolar granulation to a lesser degree. The sebaceous glands appeared to be atrophied and the hair follicles showed degeneration of the outer hair sheath. Iron was not found in the disordered apocrine glands. *G. von Bahr.*

Rheuma Test in Ophthalmology. (Il reuma-test in Oftalmologia.) DORELLO, U., and PALMIERI, L. (1960). *Arch. Ottal.*, **64**, 261. 8 refs.

A serum agglutination test which is positive in rheumatoid arthritis proved to be negative in uveitis.
Paul W. Miles.

Current Concepts of Autoimmunization: An Interpretive Review. DAMESHEK, W., SCHWARTZ, R., and OLINER, H. (1961). *Blood*, **17**, 775. 1 fig., 34 refs.

Studies in the Laboratory Estimation of Rheumatoid Arthritis Serum Factor. WINBLAD, S. (1961). *Acta path. microbiol. scand.*, **52**, 241. 31 refs.

Reaction of the Rheumatoid Factor with Human Specific Precipitates. I. AHO, K., KIRPILÄ, J., WAGER, O., and VIRKKUNEN, M. (1961). *Ann. Med. exp. Fenn.*, **39**, 66. 10 refs.

Changes in the Rheumatoid Factor in the Course of the Illness. (Veränderungen des Rheuma-faktors während der Erkrankung.) KOVÁCS, L., and BOZSÓKY, A. (1961). *Z. Rheumaforsch.*, **20**, 32. 8 refs.

Serology and Physico-chemical Characteristics of Rheumatoid Macro-globulin. Immunological and Clinical Considerations. (Sérologie et caractéres physico-chimiques de la macro-globuline rhumatoïde. Considérations immunologiques et cliniques.) SFIKAKIS, P. (1961). *Rhumatologie*, **13**, 5. 141 refs.

Studies of a Waldenström-Type Macroglobulin with Rheumatoid Factor Properties. KRITZMAN, J., KUNKEL, H. G., MCCARTHY, J., and MELLORS, R. C. (1961). *J. Lab. clin. Med.*, **57**, 905. 9 figs, 24 refs.

Carbohydrate Content of Euglobulins of Normal and Rheumatoid Sera (26 510). STARNES, W. R. (1961). *Proc. Soc. exp. Biol.* (*N.Y.*), **106**, 883. 6 figs, 10 refs.

Reaction of Rheumatoid Sera with Fragments of Papain-Digested Rabbit Gamma Globulin. GOODMAN, J. W. (1961). *Proc. Soc. exp. Biol.* (*N.Y.*), **106**, 822. 14 refs.

Attempt to Provoke Rheumatoid Factor-like Phenomenon in Rabbit Serum by Repeated Intravenous Injections of Papain. KALLIOMÄKI, J. L., AHLAS, A., MARKKANEN, T. K., PIRILÄ, and TOIVANEN, P. (1961). *Ann. Med. exp. Fenn.*, **39**, 62. 10 refs.

Antistreptolysin Activity in Chromatographic Fractions of Serum Subfractions of γ-Globulin Preparations. HEDBERG, H., and MORITZ, U. (1960). *Acta rheum. scand.*, **6**, 179. 4 figs, 16 refs.

Contribution to the Study of Hepatic Function in Rheumatoid Arthritis. Estimation of Serum Quininosidase Activity. (Contributo allo studio della funzionalità epatica in corso di artritis reumatoide. Dosaggio dell'attività chininossidasica del siero.) SEMERARO, V., and MOLLICA, N. (1961). *Progr. med.* (*Napoli*), **17**, 193. 11 refs.

Gamma Globulin Complexes in Rheumatoid Arthritis and Certain Other Conditions. KUNKEL, H. G., MÜLLER-EBERHARD, H. J., FUDENBERG, H. H., and TOMASI, T. B. (1961). *J. clin. Invest.*, **40**, 117. 8 figs, 29 refs.

Different Rheumatoid Factors in the Serum of One Patient with Rheumatoid Arthritis. HEIMER, R., SCHWARTZ, E. R., and FREYBERG, R. H. (1961). *J. Lab. clin. Med.*, **57**, 16. 10 figs, 22 refs.

Comparison of the Value of Several Serological Tests in Rheumatoid Disease. GARRY, M. W., and LOPEZ, J. F. (1961). *Amer. J. med. Sci.*, **241**, 225. 17 refs.

Quick's Hippuric Test in Children Suffering from Rheumatic Disease. (Proba hipurowa Quicka u dzieci z chorobą reumatyczną.) LIPIŃSKA-PIOTROWSKA, I., SOBIEŃ-KOPCZYŃSKA, S., and TOMCZYK, Z. (1961). *Pediat. pol.*, **36**, 263. 2 figs, 4 refs.

Simplified "Three-Step" Test in Rheumatoid Arthritis. VANSLYPE, J., TRITSMANS, E., and VERSTRAETE, J. (1960). *Acta rheum. scand.*, **6**, 202. 8 refs.

Behaviour of the Waaler-Rose and Latex-Fixation Reactions in Patients with Fibrositis. (Comportamento della reazione di Waaler-Rose e del test al lattice a goccia nei pazienti affetti da fibrosite.) EINAUDI, G., and VIARA, M. (1961). *Reumatismo*, **13**, 31.

Mechanism and Application of the Latex-Fixation Test in the Diagnosis of Rheumatoid Arthritis. I. The Nature of Serum Inhibition. (Mechanismus und Andwendung des Latex-Hemmungstests zur Diagnostik der primär-chronischen Polyarthritis. I. Über die Natur der Serum-Inhibitorem.) DEICHER, H. (1961). *Klin. Wschr.*, **39**, 612. 8 figs, 25 refs.

Photometric Reading of the Results of the Latex-Fixation Reaction. (Lecture photométrique des résultats de la réaction au latex.) LACAPÈRE, J., ARICHE, J.-J., and GAGER, A. (1961). *Rev. Rhum.*, **28**, 286. 13 figs, 3 refs.

Mechanism of Particulate Carrier Reactions. SINGER, J. M., ALTMANN, G., ORESKES, I., and PLOTZ, C. M. (1961). *Amer. J. Med.*, **30**, 772. 29 refs.

Modified Bentonite Flocculation Test with Increased Sensitivity. Results in 539 Rheumatic Disease Cases. ROWLAND PEARSALL, H., TESLUK, H., ANDERSON, D. W., and BEGGS, D. (1961). *Bull. Mason Clin.*, **15**, 1. 16 refs.

Serum Salicylate Levels in Arthritis Patients receiving Acetylsalicylic Acid, Buffered Acetylsalicylic Acid, and Salicylate with P-aminobenzoic Acid. DENKO, C. W. (1961). *Arch. interamer. Rheum.*, **4**, 5. 9 refs.

Serum Iron Level in Rheumatoid Arthritis treated with Gold. GRAUDAL, H. (1960). *Acta rheum. scand.*, **6**, 303. 12 refs.

Serum Iron and Copper Metabolism in Rheumatic Diseases. ABURAYA, T., KAWAGUCHI, O., and SAKIKAWA, C. (1961). *Tokushima J. exp. Med.*, **7**, 219. 8 figs, 10 refs.

Composition and Function of Human Synovial Connective Tissue Cells measured *in vitro*. CASTOR, C. W., and FRIES, F. F. (1961). *J. Lab. clin. Med.*, **57**, 394. 6 figs, 24 refs.

Morphology and Pathogenesis of the Fibrinoid Tissue Lesion in the Rheumatic Granuloma. (Zur Morphologie und Pathogenese des fibrinoiden Gewebeschadens im rheumatischen Granulom). ALBERTINI, A. VON (1961). *Z. Rheumaforsch.*, **20**, 1. 16 figs, 16 refs.

Morphology of the Liver in Rheumatic Syndromes. (Morfologia epatica nelle sindromi reumatiche.) BAZZANELLA, F. (1961). *Minerva med. (Torino)*, **52**, 2443. 1 fig., 18 refs.

ACTH and Other Steroids

Dexamethasone Esters in Intra-articular and Soft-tissue Injections. THOMPSON, M. (1961). *Ann. phys. Med.*, **6**, 10. 2 refs.

At the Royal Victoria Infirmary, Newcastle upon Tyne, dexamethasone *tertiary*-butylacetate, in the form of "decadron T.B.A.", was injected into the knees, ankles, and wrists of twelve patients suffering from rheumatoid arthritis. The compound was also administered to two patients with osteo-arthritis of the knees, one patient with gout, and one with systemic lupus erythematosus. In all cases the compound was used in a concentration of 4 mg. per ml. The results were compared with those obtained from the intra-articular injection of hydrocortisone acetate, 25 mg. per ml. The investigation was controlled by injecting decadron T.B.A. into one joint and hydrocortisone acetate into the contralateral joint. Assessments were made at weekly intervals until a relapse occurred. Criteria of assessment included assuagement of pain and tenderness, diminution of joint swelling, and increase in the range of movement. A similar study was also undertaken in a series of fifteen patients—thirteen with rheumatoid arthritis and two with osteo-arthrosis—prednisolone acetate, 25 mg. per ml., being administered in place of hydrocortisone. Analysis of the data revealed that in both investigations decadron T.B.A. gave better results. No side-effects were observed in either series.

When the water-soluble phosphate ester of dexamethasone, in a concentration of 4 mg. per ml., was injected into extra-articular lesions such as pericapsulitis of the shoulder, subdeltoid bursitis, and stenosing tenovaginitis the outcome was again regarded as highly satisfactory, failure to obtain relief being recorded in only one of thirty cases. The dosage ranged from 1 mg. in a case of digital inflammation associated with Heberden's nodes to 12 mg. in cases of pericapsulitis of the shoulder. Local anaesthesia was not required. A satisfactory response was noted within 24 hours, and many patients experienced relief within 6 hours. As compared with hydrocortisone, dexamethasone phosphate produced a more rapid response with a minimal degree of local irritation. In one case, however, there was an exacerbation of the symptoms of duodenal ulcer 3 days after a substantial dose of the latter compound had been injected into the shoulder capsule. *A. Garland.*

Effect of Large Doses of Prednisone on the Renal Lesions and Life Span of Patients with Lupus Glomerulonephritis. POLLAK, V. E., PIRANI, C. L., and KARK, R. M. (1961). *J. Lab. clin. Med.*, **57**, 495. 3 figs, 9 refs.

This paper, from the Presbyterian-St. Lukes, Cook County, and Research and Educational Hospitals (University of Illinois College of Medicine), Chicago, describes the results of treating 26 patients with lupus glomerulonephritis with steroids. The diagnosis was based solely on the initial renal biopsy findings and two groups of patients were studied.

The first (low-steroid) group consisted of ten patients observed from 1953 to 1955 and treated with an average of 50 mg. cortisone daily to control symptoms. All of these patients died, five within 6 months, the longest and average survival being 42 and 13·8 months respectively.

The second (high-steroid] group consisted of sixteen patients observed from 1956 to 1958 and treated with a minimum dose of 40 mg. prednisone daily for 6 months. Seven died, three within one month and the others at 5, 22, 26, and 41 months respectively. Nine are still living after 34·2 months.

Evidence was obtained by a comparison of the clinical features, renal function data, and histological findings to show that the two groups were comparable at the time of the initial renal biopsy. Renal biopsies were carefully assessed by grading the changes in the glomeruli, tubules, and interstitial tissue and vessels from 0 (normal) to 4 + (extremely severe and affecting all or almost all of the particular structures). Features considered to be evidence of active and progressive lesions included fibrinoid change, local necrosis, karyorrhexis, haematoxyphil bodies, "wire-loop" lesions, and hyaline thrombi. Serial renal histological studies to a total of 25 were carried out on eight patients in the low-steroid group and 37 on fourteen in the high-steroid group. In the former, histological evidence of activity persisted and increased in severity, whereas in the latter it was unchanged or diminished. In ten of the high-steroid group evidence of activity disappeared, although irreversible lesions such as thickening of the glomerular basement membrane and capsular adhesions persisted.

A number of complications were observed in the high-steroid group. Thus fifteen of the sixteen developed a marked Cushing's syndrome, while four had miscellaneous infections, one a perforated peptic ulcer and sub-

sequently haematemesis and melaena, five diabetes mellitus, two mental disturbances, two osteoporosis, and one an Addisonian crisis following sudden cessation of therapy.

The authors conclude that the treatment of lupus glomerulonephritis with large doses of prednisone is superior to symptomatic treatment with small doses of cortisone and prevents or delays progression of the renal lesions. *Hewett A. Ellis.*

Cataracta Complicata and Corticosteroids. The Question of a Possible Relationship between Posterior Subcapsular Cataracts and Corticosteroids. ABRAHAMSON, I. A., JR., and ABRAHAMSON, I. A., SR. (1961). *Eye, Ear, Nose, Thr. Monthly*, **40**, 266. 2 refs.

An investigation of two series of cases revealed posterior subcapsular cataracts in ten of 260 cases not under treatment with steroids, and in five of 86 cases treated with steroids. In the latter group 23 patients were found to have lens changes.

It is suggested that steroids *per se* may not be the cause of cataracta complicata and that the causal role of rheumatoid arthritis is uncertain. *J. R. Hudson.*

Examination for Posterior Subcapsular Cataracts. A Preliminary Report of Results in 45 Rheumatoid Patients treated with Corticosteroids. GORDON, D. M., KAMMERER, W. H., and FREYBERG, R. H. (1961). *J. Amer. med. Ass.*, **175**, 127. 9 refs.

Three groups of cases are considered, 45 rheumatoid arthritis patients of the author's own series, 206 rheumatoid arthritis cases of co-operating physicians, and 106 non-rheumatoid arthritis cases from the latter source. In these groups the incidence of posterior subcapsular cataracts was 9, 9, and 7 per cent. respectively.

There was no definite correlation between the occurrence of posterior subcapsular cataract and the size of the daily dose of corticosteroid or the duration of such treatment.

More extensive studies will be needed to determine what relation, if any, the occurrence of posterior subcapsular cataracts has to corticosteroid treatment in rheumatoid arthritics, or to the activity of the rheumatoid arthritis. *J. R. Hudson.*

Effects of Roentgen Irradiation on Adrenal Cortical Function in Man. SOANES, W. A., COX, R. S., JR., and MAHER, J. R. (1961). *Amer. J. Roentgenol.*, **85**, 133. 4 figs, 23 refs.

This study of the effects of *x*-irradiation on adrenal cortical function was carried out at the Letterman Army Hospital, San Francisco, on nine patients with testicular tumour who were undergoing abdominal irradiation and in whom the adrenal glands were included in the treated volumes. Adrenal function was estimated before, during, and for 3 months after the period of irradiation by determining the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids in 24-hour specimens of urine. The response to injections of ACTH was used as an additional more sensitive index of "adrenal reserve". The radiation was generated at 220 kV. and was filtered to a H.V.L. of 1·35 mm. Cu. Portals of the order of 15 × 30 cm. were used, usually as paired anterior and posterior fields, and the position of the adrenal glands was estimated with reference to the upper poles of the kidneys on a radiograph of the abdomen. The dose of radiation delivered to the adrenal glands varied between 1,569 and 3,526 r. delivered over 28 to 37 days.

Since the estimation of 17-hydrocorticosteroid excretion was found to give less erratic results than that of 17-ketosteroid excretion most of the conclusions are based on the former. The following effects were seen:

(1) There was usually an enhanced response to a 1-day injection of ACTH during the period of irradiation, this being in agreement with Selye's general adaptation syndrome and the accompanying adrenal response to stress.
(2) There was also usually some reduction in the response to a 1-day injection of ACTH after completion of irradiation.
(3) In some cases the 2-day ACTH injection test (the Thorn test) gave a lower response on the second day than on the first, this occurring especially towards the end of the period of irradiation. Normally the response on the second day is higher than on the first, so that the 2-day ACTH test may be a more sensitive gauge of the effect of irradiation.

It is concluded that to obtain more definitely significant data a similar trial should be instituted using, for example, mediastinal irradiation as a control. as it is not certain that the adrenal effect is necessarily due to direct irradiation of the adrenal glands. *I. D. H. Todd.*

Cardiovascular Function during Prolonged Corticosteroid Therapy. ROBECCHI, A., DI VITTORIO, S., and EINAUDI, G. (1960). *Acta rheum. scand.*, **6**, 241. 1 ref.

New Assessment of the Complications of Prolonged Corticotherapy. (Nouveau bilan des accidents de la corticothérapie prolongée.) LOUYOT, P., GAUCHER, A., LECLERC, J., and METZ, R. (1960). *Rhumatologie*, **12**, 275. 3 figs, 151 refs.

Pituitary-adrenal Suppression after Protracted Administration of Adrenal Cortical Hormones. PARIS, J. (1961). *Proc. Mayo Clin.*, **36**, 305. 31 refs.

Clinical and Radiological Observations on the Behaviour of the Digestive Organs in Patients undergoing Prolonged Cortisone Treatment. (Rilievi clinici e radiologici sul comportamento dell'apparato gastroenterico nei malati in trattamento cortisonico protratto.) DI VITTORIO, S., EINAUDI, G., and CHIAUDANO, M. (1961). *Reumatismo*, **13**, 9. Bibl.

Comparative Study of the Clinical and Metabolic Effects of Prednisone and Fluorocorticoids in Rheumatoid Arthritis. (Estudo comparativo dos efeitos clínicos e metabólicos dos prednosteróides e corticofluorados na artrite reumatóide.) NEBÓ, F., and SPILBORGHS, G. (1961). *Rev. Ass. méd. bras.*, **7**, 35. 2 figs, 9 refs; *Rev. argent. Reum.*, **26**, 53. 9 refs.

Systemic Corticosteroid Therapy in the Rheumatic Diseases. (La terapia corticosteroidea per via generale nelle malattie reumatiche.) ROBECCHI, A., and DI VITTORIO, S. (1961). *Minerva med.* (*Torino*), **52**, 1545. 60 refs.

New Synthetic Corticosteroids in the Treatment of Rheumatoid Arthritis. (Les nouveaux corticosteroides de synthèse dans le traitement de la polyarthrite chronique évolutive.) QUEREILHAV, H. (1960). *Rhumatologie*, **12**, 287. 40 refs.

Triamcinolone in Rheumatology. (Triamcinolona en la reumatologia.) NEBÓ, F., SPILBORGHS, G., DE SANTIS, A., and CABRAL, V. G. (1961). *Rev. argent. Reum.*, **26**, 34.

Triamcinolone Treatment of the Rheumatic Diseases. (Triamcinolona en el tratamiento de enfermedades reumáticas.) MIZRAJI, M. (1960). *Arch. interamer. Rheum.*, **3**, 556. 14 refs.

Treatment of Rheumatic Diseases in Childhood with Triamcinolone and Dexamethasone. (Zur Behandlung rheumatischer Erkrankungen im Kindesalter mit Triamcinolon und Dexamethason.) HUSCJKE, U., STOEBER, E., and KÖLLE, G. (1961). *Z. Rheumaforsch.*, **20**, 43. 19 refs.

Clinical Studies with a New Corticosteroid, 6-Alpha-Fluoro-Prednisolone (Fluprednisolone). MCMAHON, F. G., and GORDON, E. S. (1961). *Wis. med. J.* **60**, 291. 1 fig., 4 refs.

Other General Subjects

New Pyrazolone-Pyrazolidin Preparation in the Treatment of Rheumatic and Traumatic Conditions. (Considerazioni sull'uso clinico di un nuovo preparato a base di pirazolone-pirazolidina in campo reumatologica e traumatologico.) PADOVANI, P. U. (1960). *Minerva med.* (*Torino*), **51**, 3559. 20 refs.

Of the various products with an analgesic and antipyretic action, "pyramidon" (amidopyrine) and its derivatives are the most effective, but their use is strictly limited by their toxicity and tendency to provoke haematological changes. In this report from the Centro Traumatologico, Bologna, the author describes his experience with "Tomanol", a recently-introduced compound consisting of two parts of 4-*iso*propylamine-1-phenyl-2:3-dimethylpyrazolone and one part of phenylbutazone, in the treatment of 84 patients, of whom three were suffering from acute articular rheumatism, 32 from rheumatoid arthritis, two from ankylosing spondylitis, fifteen from deforming osteo-arthrosis or spondylar arthrosis, ten from periarthritis, epicondylitis, myositis or tendinitis, ten from various neuritic affections or root pain after intervention for disk hernia, and twelve from osteo-articular and muscular post-traumatic affections. The drug was administered preferably by intramuscular injection, but was also given orally or as a suppository, the dosage varying for each individual case.

Therapeutic effects were rapid and noteworthy in acute and inflammatory cases and in the reactivation phases of chronic cases, but less so in mainly degenerative forms; post-traumatic and non-articular conditions responded particularly favourably to the treatment. The author found that carefully chosen patients tolerated the remedy well, provided a diet poor in salt was given. He stresses that frequent blood counts should be performed when treatment is protracted, and patients who have suffered previously from gastric or duodenal ulcers must be treated with circumspection; all patients with active ulceration of the gastro-intestinal tract or severe cardio-renal or hepatic insufficiency were excluded from the trial. The over-all therapeutic results were as follows: very good in 41 per cent., good in 34·5 per cent., and fair in 12 per cent., while no benefit was obtained in 9·5 per cent. Side-effects, which occurred in 16·5 per cent. of the cases, included nausea, hyperacidity, and vomiting in seven cases, oedema in four, and a rash and pruritus in three. No cardiac or renal complications occurred and no case of agranulocytosis was seen.

Robert E. Lister.

Phenylbutazone and Leukaemia: a Possible Association. BEAN, R. H. D. (1960). *Brit. med. J.*, **22**, 1552. 4 figs, 5 refs.

The author of this paper from the Repatriation General Hospital, Heidelberg, Victoria, Australia, describes six cases of leukaemia occurring in elderly males who had all recently been treated with phenylbutazone. The dosage and duration of treatment had varied from 10 g. given over a 3-week period to several hundred grammes given over 4 years. In one case there appeared to be a definite progression from an early toxic reaction to the development of myeloid leukaemia and death therefrom 18 months later. All the patients were rather poorly nourished and three had tuberculosis. Hypogammaglobulinaemia was found in two cases. In three of the more acute cases the morphology of the peripheral blood and bone marrow was atypical, aplasia and haemolysis being present. Lymphatic proliferation predominated in three. In all but one case the leukaemic phase was extremely short and treatment produced at best only transitory improvement.

A. Ackroyd.

Oxyphenbutazone ("Tanderil", G 27202): an Antirheumatic Derivative of Phenylbutazone. KELLY, M. (1961). *Med. J. Aust.*, **1**, 851. 17 refs.

Phenylbutazone has proved useful in the treatment of rheumatic disorders and toxic effects appear to be uncommon provided the dosage does not exceed 400 mg.

a day and it it is not given to aged patients or those with dyspepsia or cardiac disease. Nevertheless, side-effects do occur from time to time and in the search for a non-toxic derivative with the same antirheumatic action two substances of interest have been synthesized, both of which are metabolites of phenylbutazone. One of these, oxyphenbutazone (G 27202; "Tanderil"), has been found to have, like phenylbutazone, antirheumatic properties, its effect on the inflammation of acute gout being especially striking, although it has no effect on the excretion of uric acid. The other drug, G 28315, has no clinical effect on acute gout, but it is powerfully uricosuric.

The purpose of the present communication is to record the author's clinical observations with tanderil. He considers that its effect is so striking that rigidly controlled trials are unnecessary. In a daily dosage of 300 mg. he found the substance to be less toxic, but also less effective, than phenylbutazone. A dosage of 800 mg. daily for 3 consecutive days in every 6 was tried in 43 cases—thirteen of rheumatoid arthritis, two of osteoarthritis, seventeen of local fibrositis, and eleven of multiple fibrositis. Patients reported by telephone on their rheumatic symptoms and general well-being. In more than one-half of the group the effect was "striking" and in one-quarter it was as good as that of phenylbutazone. Nine patients reported toxic effects. A dosage of 600 mg. daily for 5 days of each week was tried on fifty patients suffering from similar disorders. A rather smaller proportion gave a "striking" response than with the 800-mg. dosage, but toxic symptoms occurred in only six cases.

[The author's reasons for not accepting the need for a controlled therapeutic trial are not convincing. His figures purporting to show a difference in toxic effects and in the proportion showing "striking" improvement between the 600-mg. and 800-mg. dosage schemes are not statistically significant.] *Kenneth Stone.*

Rheumatic Phlebitis of the Coronary Veins. VON GLAHN, W. C., and KUSCHNER, M. (1961). *Amer. J. Path.*, **38**, 251. 6 figs, 12 refs.

Writing from Louisiana State and New York University Schools of Medicine, the authors briefly review the literature of rheumatic phlebitis. They then describe a type of lesion of the coronary sinuses found in cases of active rheumatic heart disease. The material used consisted of nineteen histological sections from eighteen cases of active rheumatic heart disease which included the coronary sinus. This was compared with comparable material from 35 individuals without evidence of rheumatic disease.

Of the eighteen cases of rheumatic disease, lesions were present in the coronary sinus in ten, An acute inflammatory reaction of the sinus was found in eight cases, in five of which Aschoff bodies were also present in the adventitia. Aschoff bodies were seen in the adventitia without other reaction in one case. In three cases there were bands of eosinophilic material in the intima and an acute inflammatory reaction with Aschoff bodies in the adventitia. The lesions involved only sectors of the sinus wall and in structure closely resembled those of rheumatic endocarditis. No thromboses were present. Healed lesions were seen in five cases, in four of which there were also acute lesions. The phlebitis apparently developed and healed rapidly and the presence of acute and healed lesions in the same sinus indicated that the vessel was being damaged repeatedly. None of the controls showed similar lesions. *R. Wyburn-Mason.*

Relief of Pain by Cooling of the Skin. ELLIS, M. (1961). *Brit. med. J.*, **1**, 250. 5 refs.

The author describes his experience extending over a period of 9 years at the General Infirmary at Leeds of skin cooling by ethyl chloride spray in the treatment of various painful conditions. In acute lumbago 20 to 30 seconds' spraying of the lumbar region causes the scoliosis and pain to disappear. Rest in bed for a number of days is advised before return to work, although some patients are able to return the same or the following day. Chronic low backache does not respond quite so dramatically. Acute torticollis is relieved by this treatment, and it is claimed that a single application may relieve pain in patients with fibrosis, painful scars, and causalgia. In renal colic application of the spray from the renal angle to the pubes gives immediate relief, but the treatment may have to be repeated as the stone passes down the ureter. Similarly, dysmenorrhoea can be relieved by spraying the hypogastrium for 15 to 20 seconds. In cases of fractured rib treated by local infiltration of procaine prolonged relief of residual pain is obtained by this method of skin cooling.

The author discusses the rationale of the treatment and suggests that there is a competitive inhibition between cold and pain impulses in the central pain receptor areas.

It is emphasized that the skin should be cooled and not frozen (the usual type of spray is not ideal for this) and that all the skin of the appropriate dermatome should be cooled for 15 to 30 seconds. Since ethyl chloride is inflammable, toxic, and anaesthetic, a new inert liquid in a spray pack "skefron" has been tried, with comparable results. *J. B. Millard.*

Operative Traumata evidencing Rheumatic Uveitis. (Traumatismes opératoires localizateurs d'uvéite rhumatismale.) ALGAN, B. (1960). *Bull. Soc. Ophtal. Fr.*, p. 486.

The author reports two cases of rheumatic uveitis appearing after cataract extraction. The uveitis was torpid and in each case the patient had had polyarthritis some years before. *J. Rougier.*

Examination of the Blood Pressure in the Central Retinal Artery of Rheumatic Patients. [In Russian.] KOLMAKOVA, A. E. (1961). *Vestn. Oftal.*, No. 1, p. 34. 29 refs.

Rheumatism is an illness of the cardiovascular system and capillary-connective tissue and so is classified as a collagen disease. The author has performed ophthalmodynamometry on 32 rheumatic patients and discusses the significance of the findings. [It is not clear what the author means by "rheumatism".] *B. Jay.*

Scleromalacia Perforans and Massive Granuloma of the Sclera. A Report of an Unusual Combination of Ocular Pathology in Rheumatoid Arthritis. WOLTER, J. R., and BENTLEY, M. D. (1961). *Amer. J. Ophthal.*, **51**, 71. 21 figs, 9 refs.

Two cases of rheumatoid arthritis which show a combination of scleromalacia perforans and massive granuloma of the sclera are reported. Histological findings are given and both lesions are considered to be ocular manifestations of rheumatoid arthritis.

M. C. Handscombe.

Ocular Disorders associated with Deforming Rheumatism. (Manifestations oculaires associées au rhumatisme déformant.) APPELMANS, —. (1960). *Bull. Soc. Ophtal. Fr.*, p. 477.

An Appraisal of Intra-Articular Phenylbutazone. PIERIK, M. G., and O'CONNELL, W. J. (1961). *R.I. med. J.*, **44**, 281. 1 ref.

"Depo-Medrol" in Rheumatology. (Le dépo-médrol en rhumatologie.) VIGNON, G., MAÎTREPIERRE, J., VOLLE, L., and REVILLARD, J.-P. (1961). *Lyon med.*, p. 121.

Tanderil (G 27202) in the Treatment of the Rheumatic Diseases. JARLØV, N. V. (1960). *Acta rheum. scand.*, **6**, 174. 3 refs.

Value of Nialamide in the Treatment of Diseases of the Rheumatic Group. (Bedeutung des Niamid in der Behandlung der Krankheiten des rheumatischen Formenkreises.) KRAMMER, F. (1961). *Wien. med. Wschr.*, **111**, 353.

Pharmacological Testing of Antiphlogistic and Anti-rheumatic Substances. HABERLAND, G. L. (1960). *Arch. interamer. Rheum.*, **3**, 473. 3 figs, 20 refs.

Clinical Study of the Anti-rheumatic Activity of a Preparation containing Zoxazolamine, Salicylamide, and Vitamin B_1. (Richerche cliniche sull'attivita anti-reumatica di una associazione, zoxazolamina-salicil-amide-vitamin B_1.) GIACHI, E. (1961). *Settim. med.*, **49**, 265. 24 refs.

Abdominal Rheumatism. (Der Weichteil-Rheumatismus.) BÄKER, A. (1961). *Med. Welt*, **1961**, 1140. 1 fig., 9 refs.

Rheumatoid Lung Disease: A Case Report which includes Respiratory Studies and a Lung Biopsy. CUDKOWICZ, L., MADOFF, I. M., and ABELMANN, W. H. (1961). *Brit. J. Dis. Chest*, **55**, 35. 4 figs, 14 refs.

Some Aspects of Roentgen Diagnosis of the Connective Tissue Diseases. SOILA, P. (1960). *Acta rheum. scand.*, **6**, 283. 4 figs, 12 refs.

Rheumatoid Disease. GRESHAM, G. A. (1961). *Rheumatism*, **17**, 35. 23 refs.

Presentation of a Decimal Scale based on Four Criteria permitting the Evaluation of a Synthetic Measure of Functional Capacity in Rheumatology. (Présentation d'un barème décimal a quatre critériums (le T.A.P.I.) permettant l'évaluation d'un taux synthétique de capacités fonctionnelles en rhumatologie.) VERHAEGHE, A., and LEBEURRE, R. (1961). *Rev. Rhum.*, **28**, 145.

Disease Classification for a Department of Rheumatism. FLETCHER, E. T. D., and COKE, H. (1961). *Rheumatism*, **17**, 28.

Pseudo-Chondrodystrophia Rheumatica ("Rheumatic Dwarfism"). BRULAND, H. (1960). *Acta rheum. scand.*, **6**, 209. 19 figs, 71 refs.

Carpal-Tunnel Syndrome—Initial Manifestation of Systemic Disease. GROSSMAN, L. A., KAPLAN, H. J., OWNBY, F. D., and GROSSMAN, M. (1961). *J. Amer. med. Ass.*, **176**, 259. 7 refs.

Acetylsalicylic Anhydride in the Treatment of Rheumatic Diseases. (L'anidride acetilsalicilica nella cura delle malattie reumatiche.) BACCARINI, V. (1961). *Clin. ter.*, **20**, 62. 2 figs, 11 refs.

Experience with High Doses of "Osadrin" in the Treatment of Rheumatic Diseases. (Erfahrungen mit hohen Dosen von Osadrin bei Behandlung Rheumakranker.) BECKSCHÄFER, W. (1961). *Munch. med. Wschr.*, **7**, 369. 9 refs.

Assessment of Activity of the Rheumatic Process by means of the "Trafuril" Reaction. (Ocena aktywnosci procesu reumatycznego u dzieci w oparciu o wyniki odczynu trafurylowego.) LEWENFISZ-WOJNAROWSKA, T., and ZAORSKA, B. (1960). *Pediat. pol.*, **35**, 1289. 23 refs.

Observations on the Syndrome of Mafucci-Kast. (Remàrques a propos d'un cas de syndrome de Mafucci-Kast.) PIGUET, B., and MEDIONI, L. (1961). *Rev. Rhum.*, **28**, 27. 7 figs, 17 refs.

Study of Focal Infection in Rheumatic Diseases and True Focal Rheumatism. (Estudio sobre el foco de infección en las enfermedades reumáticas y el reumatismo focal verdadero.) ROTÉS QUEROL, J., and ROIG ESCOFET, D. (1960). *Rev. esp. Reum.*, **7**, 515. 22 refs.

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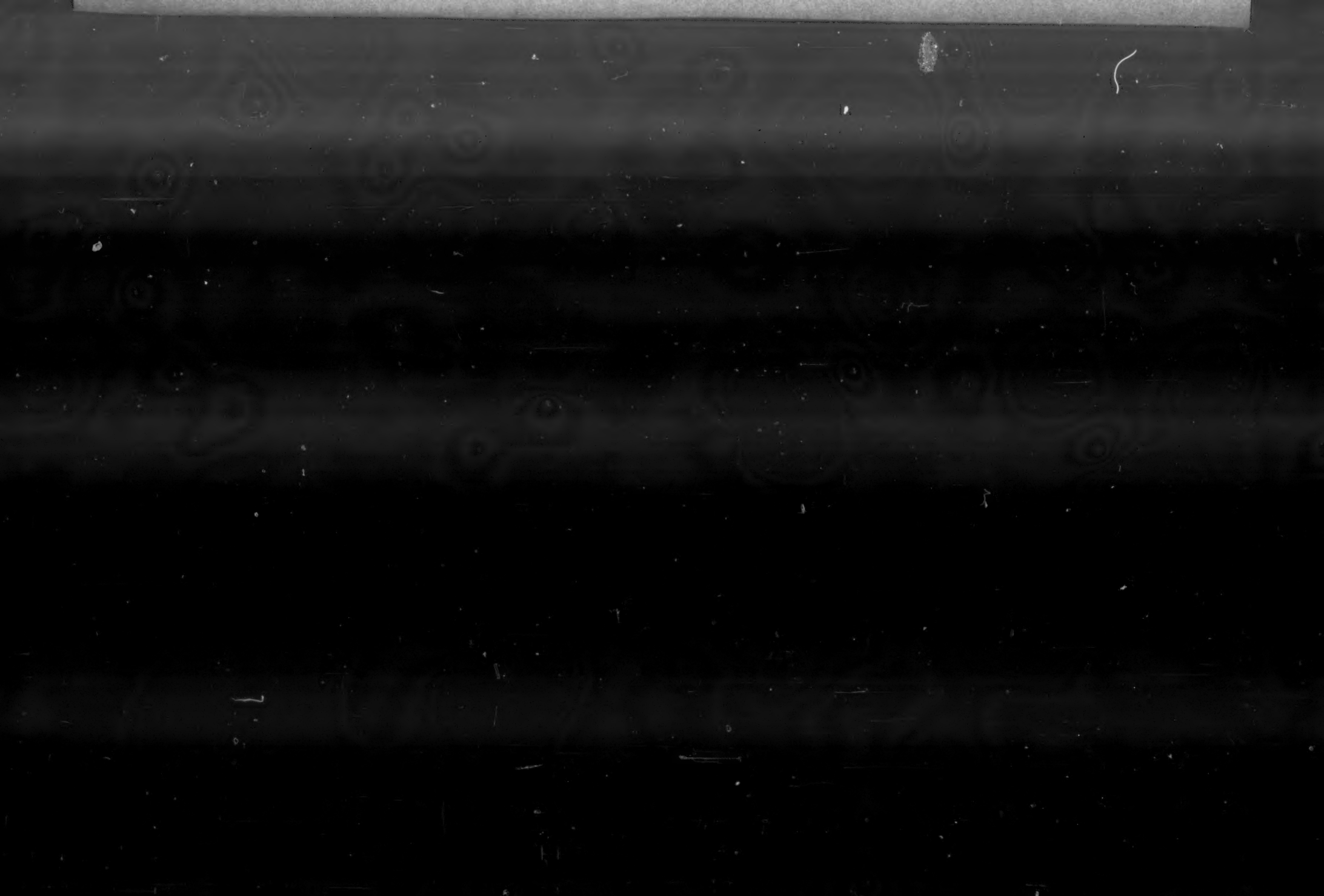

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